THE ACTION OF HYDROFLUMETHIAZIDE IN RELATION TO ADRENAL STEROIDS AND POTASSIUM LOSS

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AN increase of potassium excretion associated with a fall in the serum-potassium level is one of the more serious problems encountered with diuretic therapy.

Considerable potassium loss may sometimes be produced by mercurial diuretics (Cort and Matthews 1954), but the introduction of the benzothiadiazine diuretics has brought this hazard into prominence (Bayliss et al. 1958, Read et al. 1958). A similar phenomenon has been described with acetazolamide, and was attributed to diminished production of hydrogen ions—resulting from carbonic anhydrase inhibition (Counihan et al. 1954)—which led to potassium instead of hydrogen ions being exchanged for sodium in the distal renal tubules. As chlorothiazide is chemically similar to acetazolamide and can inhibit carbonic-anhydrase, the potassium loss it produces has been explained in the same way (Pitts et al. 1958). However, this cannot be the only mechanism involved, since some of the new oral diuretics—in particular, hydrochlorothiazide and hydroflumethiazide—may cause hypokalæmia when used in doses which do not increase urinary bicarbonate (Fleming et al. 1959, Kerr et al. 1959, Edmonds and Wilson 1959).

The well-known influence of adrenal steroids on sodium and potassium excretion, together with the frequent finding of abnormality in aldosterone excretion in clinical states in which diuretics are used, suggested that the level of circulating steroids may partly determine the relative amounts of sodium and potassium lost during the diuresis. To test this hypothesis, we have studied the composition of the urine of two normal subjects after administration of hydroflumethiazide, under conditions designed to vary the degree of renal stimulation by salt-retaining hormones. This variation was achieved either with diets high or low in salt, which are known to alter the endogenous secretion of aldosterone (Axelrad and Luetscher 1954, Mulrow et al. 1956), or by giving large doses of fludrocortisone with a normal diet. Fludrocortisone was used because a sufficiently large supply of aldosterone was not obtainable; but the action of the two substances is similar.

Additional evidence was obtained by using a steroidal spirolactone, SC-9420 (Searle). The spirolactones probably antagonise the action of aldosterone and related steroids on the renal tubular cells (Liddle 1958). We used SC-9420 because it is well absorbed when taken by mouth and is without untoward side-effects. Our results support the view that its most important effects are due to antagonism of sodium-retaining steroids and that the activity of these steroids is chiefly responsible for the excess potassium loss observed with hydroflumethiazide under certain conditions.

Methods

Most of the observations were made on two normal men, aged 29 and 42; but in addition the course of action of the spirolactone was studied in two other healthy men aged 22 and 23. They continued their customary hospital and laboratory duties during the experiments.

Either a normal diet was taken, or a special diet providing only about 1 g. of sodium chloride daily. When a high salt intake was required, 20 g. of sodium chloride daily was added to the normal diet. Fluid intake was unrestricted. The subjects were weighed daily.

The following substances were taken by mouth during the experiments: hydroflumethiazide 50 mg. thrice daily, at 8 A.M., 4 P.M., and midnight; spirolactone SC-9420 either 100 mg. or 200 mg. four-hourly beginning at 6 A.M. to a daily total of 400 mg. or 800 mg.; and fludrocortisone acetate either 0·5 mg. twice daily or 1 mg. thrice daily, the doses in both cases being evenly spaced over the twenty-four hours beginning at 8 A.M.

Urine collections were made over twenty-four-hour periods beginning at 8 A.M.

Sodium and potassium in serum and urine were measured by flame photometry, chloride by potentiometric titration (Sanderson 1952) and creatinine in serum and urine by the method of Owen et al. (1954).

Results

Normal Salt Intake and Fludrocortisone

The aim of these experiments was to determine the effect of a standard dose of hydroflumethiazide on the excretion of electrolytes when the subjects were on a normal diet and when a potent sodium-retaining steroid was administered. Spontaneous variations in electrolyte excretion were studied during a week before any treatment was given and subsequently on control days before the administration of drugs (fig. 1 and table I). The changes induced by the diuretic and by fludrocortisone greatly exceeded the spontaneous fluctuations.

After urine collections on two control days, hydroflumethiazide 150 mg. daily was started and continued for three days.

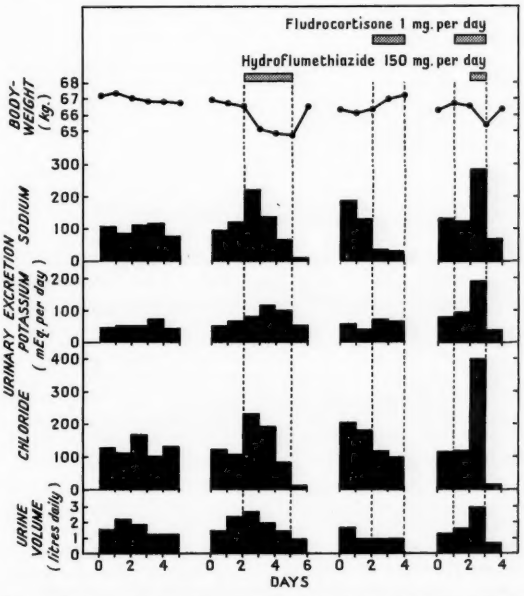

Fig. 1—Action of hydroflumethiazide and fludrocortisone acetate on urine volume and sodium, potassium, and chloride excretion in subject 1 on a normal diet.

TABLE I—INFLUENCE OF FLUDROCORTISONE ON DAILY SODIUM, POTASSIUM, AND CHLORIDE EXCRETION WHEN HYDROFLUMETHIAZIDE WAS GIVEN TO SUBJECT 2 ON A NORMAL DIET

The fludrocortisone was given in two-day courses and when hydroflumethiazide was added it was given on the second day. The general plan of the experiments is shown in figs. 1 and 2 (mean ±S.D.).

Treatment (doses per day)	Sodium (mEq.)	Potassium (mEq.)	(Na+K) (mEq.)	Na/K	Chloride (mEq.)
Mean of 15 control days	133 ±31·9	83 ±16·8	216	1·6	133 ±41·9
Fludrocortisone 1 mg. (2nd day)	14·0	51·6	66	0·27	42·8
Fludrocortisone 3 mg. (2nd day)	4·5	117	121	0·04	40·5
Hydroflumethiazide 150 mg.	343	113	456	3·03	340
Hydroflumethiazide 150 mg. Fludrocortisone 1 mg.	224	185	409	1·21	347
Hydroflumethiazide 150 mg. Fludrocortisone 3 mg.	174	240	414	0·73	355

On the first day that the drug was given, both subjects showed a great increase in water, sodium, and chloride excretion, accompanied by a fall in body-weight; but potassium excretion was only slightly enhanced. On the subsequent days, sodium and chloride excretion fell to a level similar to that seen before the diuretic was given, but potassium excretion remained slightly elevated (fig. 1). On stopping the diuretic there was sodium and chloride retention and a rise in body-weight.

Two weeks later, the effect of fludrocortisone was studied. Urine was collected for two days without any treatment and then fludrocortisone 0·5 mg. twice daily was given for two days. Both sodium and chloride excretion fell but the fall of chloride was appreciably less than that of sodium. Potassium excretion increased slightly and body-weight rose. After a further two weeks, the experiment was repeated but on this occasion hydroflumethiazide 150 mg. was given on the second day of the fludrocortisone administration. The action of the diuretic on chloride excretion was not inhibited by the fludrocortisone but there was a definite change in proportions of the two cations. Potassium loss was consistently increased and the Na/K ratio altered.

The experiments were then repeated with the amount of fludrocortisone raised to 3 mg. daily (fig. 2 and table I). This dose reduced sodium and chloride excretion to a very low level although again the depression of chloride was less than that of sodium. When hydroflumethiazide was given along with the bigger dose of fludrocortisone a large diuresis of chloride again ensued. This chloride was accompanied by sodium and potassium, but the excretion of the latter was even further enhanced.

Action of the spirolactone, SC-9420.—The experiments using fludrocortisone 3 mg. daily were repeated to determine whether the effects on cation excretion could be reversed by the administration of the spirolactone.

The course of action of a single dose of spirolactone 200 mg. given during fludrocortisone administration is shown in fig. 3. Sodium and chloride excretion rose slightly within two to four hours and then rapidly to a maximum between six and eight hours. The effect had disappeared after twenty-four hours. Similar results were obtained in three other subjects.

When the spirolactone was given alone in a daily dose of either 400 mg. or 800 mg. to the subjects on a normal diet, there was only a small rise of sodium and chloride excretion (fig. 2 and table II). When, however, 400 mg. of the spirolactone was taken on the second day of fludrocortisone administration, sodium excretion rose considerably and chloride moderately. The effect of the fludrocortisone had been largely reversed. On the second day of a further course of fludrocortisone 3 mg. daily, hydroflumethiazide 150 mg. and spirolactone 400 mg. were taken. Sodium, potassium, and chloride excretion rose, but the rise of sodium compared with potassium was much greater than that observed when the spirolactone was omitted (fig. 2 and table II). The total (Na+K) excretion and chloride excretion, however, were not significantly altered.

As the effect of the fludrocortisone was not completely reversed by 400 mg. of spirolactone, the experiments were done once more in the same way but with the dose of spirolactone increased to 800 mg. In these circumstances, in subject 1, the potassium loss following the diuretic was even further reduced so that sodium and chloride were excreted in nearly equivalent amounts. In subject 2, however, this dose was still insufficient to reverse completely the effect of fludrocortisone on the hydroflumethiazide-induced diuresis.

High Salt Intake

With a high salt intake the findings in the two subjects were essentially similar.

The addition of sodium chloride 20 g. daily to the normal diet produced an increase in body-weight and a rise in urine volume and in sodium and chloride excretion (fig. 4). Subject 1 showed a slight increase in potassium excretion as sodium excretion rose during the first two days on the increased salt intake, but thereafter it fell to the previous level. Subject 2 had no comparable increase of potassium excretion.

When hydroflumethiazide was given there was a considerable increase in urine volume and in sodium and chloride excretion;

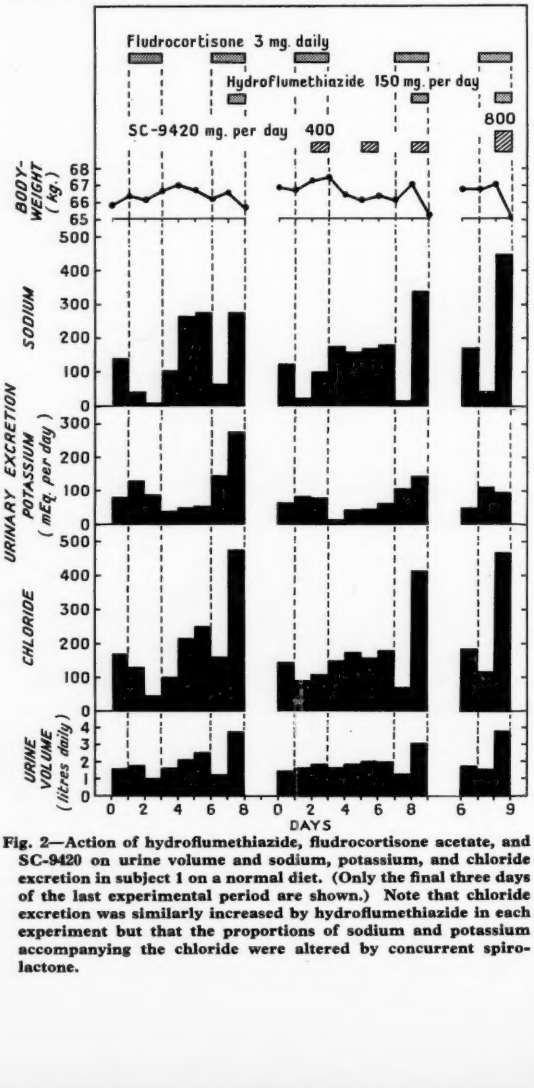

Fig. 2—Action of hydroflumethiazide, fludrocortisone acetate, and SC-9420 on urine volume and sodium, potassium, and chloride excretion in subject 1 on a normal diet. (Only the final three days of the last experimental period are shown.) Note that chloride excretion was similarly increased by hydroflumethiazide in each experiment but that the proportions of sodium and potassium accompanying the chloride were altered by concurrent spirolactone.

body-weight fell to a level a little below that recorded in the period preceding the high salt intake. After the first day of hydroflumethiazide, sodium and chloride excretion returned to a level balancing intake, and it continued unchanged during the rest of the period of diuretic administration. Body-weight also remained constant after the initial fall. There was no alteration in daily potassium excretion when the diuretic was given. As soon as the diuretic was stopped, there was a fall in urine volume, and in sodium and chloride excretion associated with a rise in body-weight. Again, potassium excretion was unchanged.

Serum electrolytes altered only slightly during these experiments (table III). Both subjects showed a slight increase in serum sodium and chloride levels when the salt intake was increased, with a tendency to fall again during the diuretic administration. The serum-potassium level showed no significant changes in either subject.

TABLE II—EFFECT OF SPIROLACTONE SC-9420 ON DAILY SODIUM, POTASSIUM, AND CHLORIDE EXCRETION WHEN GIVEN ALONE OR WITH FLUDROCORTISONE AND HYDROFLUMETHIAZIDE (SUBJECT 2).

The general plan of the experiment is shown in fig. 2.

Treatment (doses per day)	Sodium (mEq.)	Potassium (mEq.)	(Na+K) (mEq.)	Na/K	Chloride (mEq.)
SC-9420 400 mg.	189	83	272	2·28	172
SC-9420 800 mg.	192	79	271	2·43	176
SC-9420 400 mg. Fludrocortisone 3 mg. . .	57	79	136	0·72	78
SC-9420 800 mg. Fludrocortisone 3 mg. . .	113	83	196	1·36	115
SC-9420 400 mg. Fludrocortisone 3 mg. Hydroflumethiazide 150 mg.	347	159	506	2·18	426
SC-9420 800 mg. Fludrocortisone 3 mg. Hydroflumethiazide 150 mg.	301	144	445	2·09	376

Endogenous creatinine clearance was used as a measure of glomerular filtration rate and showed only small changes. In both subjects, glomerular filtration rate was greater during the period of high salt intake but fell slightly when the diuretic was given. Daily creatinine excretion showed little variation.

Low Salt Intake

In these experiments, each subject spent three periods on a low salt diet.

On the morning of the first day of the diet, a single dose of hydroflumethiazide 100 mg. was given, and as a result the body-weight fell by about 1 kg. Subsequently, it was maintained at this level by the low-salt diet. The urinary excretion of sodium and chloride became very low. On the first occasion, subject 1 remained on the diet for nine days and subject 2 for six days. After the first three days, hydroflumethiazide 150 mg. daily was begun. The results were similar in the two subjects, and details of subject 1 only are shown (fig. 5). Chloride excretion rose considerably, but this rise was accompanied mainly by potassium and the rise of sodium excretion was small. The excretion of sodium, potassium, and chloride then gradually fell despite continued administration of the diuretic. The decrease in sodium loss was particularly obvious, but the daily excretion of potassium and chloride remained above the control level throughout the period of treatment with hydroflumethiazide. When the diuretic was stopped, there was an immediate conservation of potassium, the excretion-rates falling well below those observed during the initial two control days on the low-salt diet (fig. 5). Body-weight fell when the diuretic was given and then stabilised at a new level. It rose rapidly when salt was reintroduced into the diet.

Serum sodium and chloride concentrations were slightly depressed during the period on the low salt intake. In both subjects there was a conspicuous fall in serum-potassium level during the diuretic treatment (table III). Creatinine clearance was depressed during the low-salt regime and fell further when the diuretic was given. Daily creatinine excretion showed little variation.

At intervals of several weeks, the experiments were repeated in the same way except that the period on the low-salt diet was reduced to four days. The pattern of body-weight changes and of sodium, potassium, and chloride excretion on the first three days was similar in all the experiments. In the second experiment, the subjects took the spirolactone alone on the fourth day (fig. 5). Sodium excretion increased but body-weight and potassium and chloride excretion were unchanged. The course of action of the spirolactone was also examined while the subjects were on a low-salt diet. It was similar in the two subjects, and the results for subject 1 are reproduced in fig. 6. Sodium excretion increased after a delay of four to six hours and reached a maximum in ten to twelve hours.

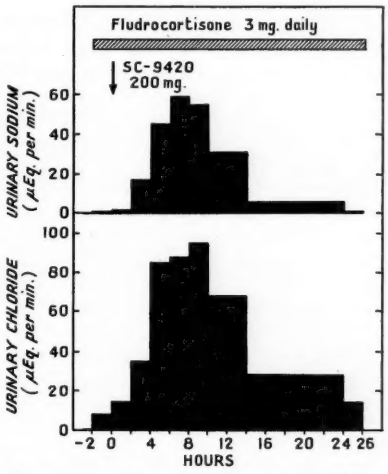

Fig. 3—Effect of a single oral dose of SC-9420 on sodium and chloride excretion in subject 1 on the second day of fludrocortisone treatment.

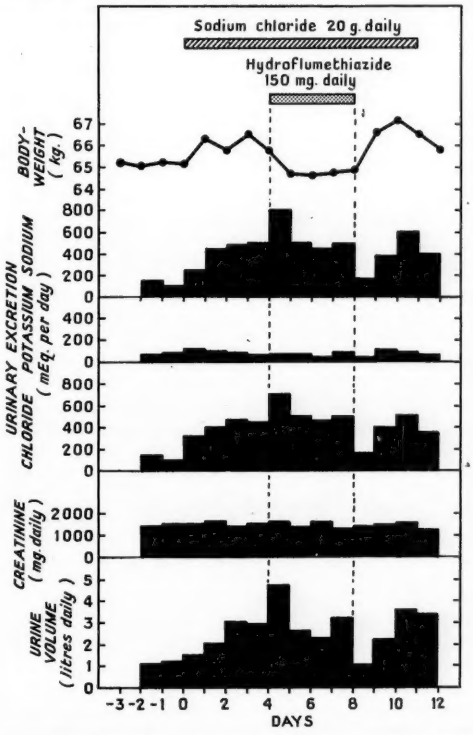

Fig. 4—Action of hydroflumethiazide on urine volume, sodium, potassium, chloride, and creatinine excretion of a normal subject on a high salt intake (sodium chloride 20 g. daily added to a normal diet).

TABLE III—CREATININE CLEARANCE AND SERUM ELECTROLYTES OF TWO NORMAL SUBJECTS ON VARIOUS DIETS AND TREATED WITH HYDROFLUMETHIAZIDE

Diet was started on day 0 in all cases

—	Treatment (doses per day)	Diet	Day	Creatinine clearance (ml. per min.)	Sodium (mEq. per l.)	Potassium (mEq. per l.)	Chloride (mEq. per l.)
Subject 1	None	Normal	−1	110	139	4·2	106
	Hydroflumethiazide 150 mg. on days 4–7	High-salt	1	124	143	4·2	111
			3	120	140	4·3	103
			6	115	140	4·3	102
			9	110	138	4·5	108
			11	117	140	4·5	110
	Hydroflumethiazide 150 mg. on days 3–8	Low-salt	2	93	138	4·0	104
			5	102	136	3·7	100
			8	88	136	3·4	99
Subject 2	None	Normal	−1	115	140	4·2	105
	Hydroflumethiazide 150 mg. on days 4–8 and 16–18	High-salt	2	127	143	4·2	111
			7	132	143	4·1	108
			18	123	144	4·4	106
	Hydroflumethiazide 150 mg. on days 3–5	Low-salt	2	101	140	3·9	99
			5	91	138	3·1	97

In the final experiment, hydroflumethiazide 150 mg. was taken during the fourth day in addition to the spirolactone (fig. 5). The increase in chloride excretion and the fall in body-weight closely resembled that observed when hydroflumethiazide was taken alone, but the pattern of excretion of the cations was strikingly different. The proportion of sodium was considerably greater than previously and of potassium much less. The total excretion (Na+K), however, was similar in the two experiments and balanced the increase of chloride ions.

Discussion

There was considerable variation in the relative proportions of sodium and potassium accompanying the increased excretion of chloride induced by hydroflumethiazide. The ratio between the two cations was chiefly influenced by the amount of endogenous or exogenous sodium-retaining steroids present at the time. It is generally considered that most, if not all, of the potassium filtered by the glomerulus is reabsorbed, and that the excreted potassium comes from exchange with sodium ions in the distal renal tubule (Berliner et al. 1951). This exchange depends on the presence of sodium ions within the tubular lumen, the availability of potassium, and the supply of adrenal steroids. On a low-salt diet, potassium excretion is not excessive although secretion of aldosterone is considerably increased. Moreover, administering large quantities of sodium-retaining steroids to animals on a low-salt intake does not produce potassium depletion (Seldin et al. 1951, Relman and Schwartz 1952), in contrast to their action in animals on a normal salt intake. The probable explanation of these findings is that when sodium-chloride excretion is very low, as on a reduced salt intake, little sodium and chloride reaches the distal tubular region where cation exchange occurs, and consequently the exchange is limited.

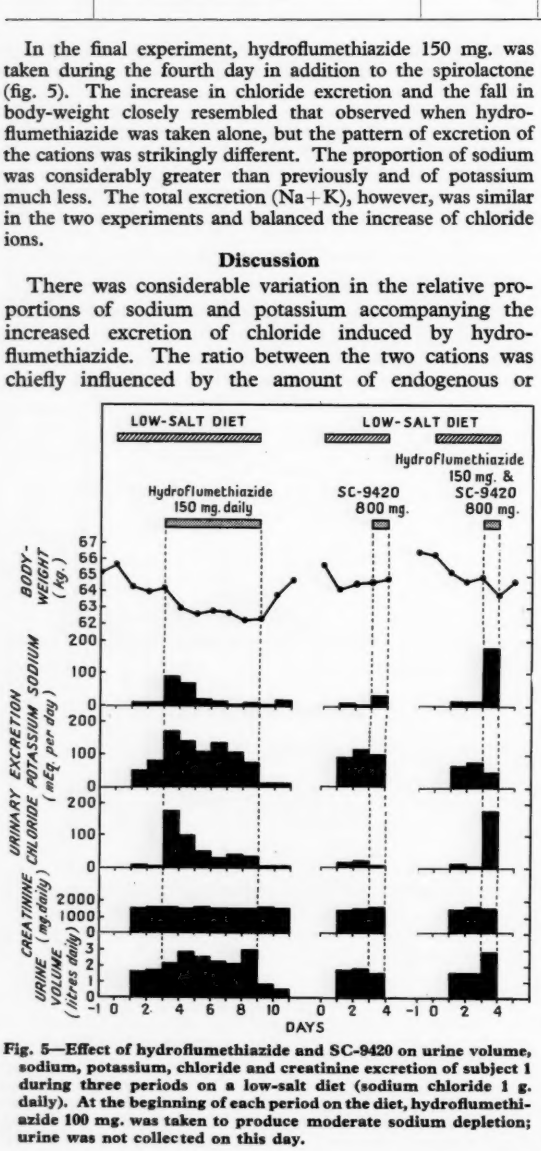

Fig. 5—Effect of hydroflumethiazide and SC-9420 on urine volume, sodium, potassium, chloride and creatinine excretion of subject 1 during three periods on a low-salt diet (sodium chloride 1 g. daily). At the beginning of each period on the diet, hydroflumethiazide 100 mg. was taken to produce moderate sodium depletion; urine was not collected on this day.

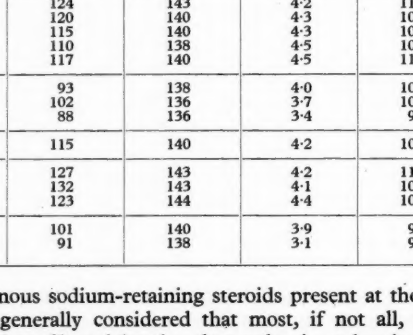

Fig. 6—Effect of the spirolactone, SC-9420, on sodium and chloride excretion in subject 1 on a low-salt diet (about 1 g. sodium chloride daily).

There is experimental evidence that the benzothiadiazine diuretics act proximally to the cation-exchange region, probably on the proximal renal tubule (Vander et al. 1959). Our results are consistent with this view. The action on the proximal site results in the delivery of increased quantities of sodium and chloride to the distal region. When the level of circulating sodium-retaining steroids is low, as on a high salt intake, or when their action is antagonised by spirolactone, there is little increase in the exchange and potassium excretion is unaltered. When, however, the exchange mechanism is stimulated by sodium-retaining steroids, potassium loss becomes excessive. These conditions obtain when the

diuretic is given during a period of salt restriction or when fludrocortisone is given concurrently.

Our results show that fludrocortisone has a dual effect on sodium metabolism in the kidney. It causes an increase in sodium and chloride reabsorption and also encourages the exchange of sodium for potassium ions. The extent of the potassium loss will depend on the balance of these two actions. If the action of fludrocortisone on sodium and chloride reabsorption predominates, few of these ions reach the region of the renal tubule where the cation exchange takes place. Thus only limited exchange of sodium for potassium ions can occur, even though the mechanism is under stimulation by fludrocortisone.

The increase in chloride excretion induced by hydroflumethiazide in our experiments was unaffected by the simultaneous administration of fludrocortisone. This suggested that, although the diuretic antagonised or masked the sodium and chloride reabsorbing action of fludrocortisone, it had no effect on the sodium-potassium exchange mechanism, which remained under the influence of the steroid.

When the spirolactone was given alone to a subject on a normal diet, it had little effect. When, however, it was given with fludrocortisone, the effects of the latter were reversed. This supported the evidence of other workers (Liddle 1958, Ross and Bethune 1959) that the effects of this substance are principally, if not entirely, the result of antagonism of the actions of sodium-retaining steroids.

The reciprocal changes in sodium and potassium ions observed in our experiments strongly suggested that the phenomena resulted from a sodium-potassium exchange and that this was considerably influenced by sodium-retaining steroids.

It was consistently observed that, despite continued administration of the diuretic over several days, the excessive loss of sodium and chloride always ceased and the body-weight stabilised at a new lower level. This level, however, was appreciably lower on the low-salt diet than on the high-salt diet. When the diuretic was discontinued, the excretion of sodium and chloride fell abruptly. Apparently some factor antagonised the action of the diuretic on sodium and chloride excretion and persisted after the diuretic was withdrawn. The explanation is still uncertain. The changes in serum electrolytes and glomerular filtration rate were small, and it is difficult to believe that they were responsible for the diminished excretion. Nor did it seem likely that adrenal steroids were responsible, since the potent sodium-retaining steroid, fludrocortisone, did not antagonise the diuretic even in large doses.

Summary

The action of a benzothiadiazine diuretic, hydroflumethiazide, has been studied in two normal subjects. With the subjects on a normal diet, hydroflumethiazide increased the excretion of water, sodium, and chloride and to a small extent of potassium. When fludrocortisone was given concurrently, the potassium loss was greatly increased. The spirolactone SC-9420, which is an aldosterone antagonist, reversed this effect of fludrocortisone.

With the subjects on a high salt intake (20 g. sodium chloride added daily to the normal diet), which leads to a low endogenous secretion of aldosterone, hydroflumethiazide produced a large diuresis of sodium, chloride, and water and a fall of body-weight. Potassium excretion was unaffected and the serum-potassium level was unchanged.

With the subjects on a low salt intake (about 1 g. sodium chloride daily), which causes a high endogenous secretion of aldosterone, hydroflumethiazide produced a rise of chloride excretion accompanied mainly by potassium; the rise of urinary sodium was small. The serum-potassium level fell. If the aldosterone antagonist was given concurrently with the diuretic, potassium excretion was much less and sodium appeared in its place.

The extent of the potassium loss following the administration of hydroflumethiazide is related to the activity of sodium-retaining steroids. If the exogenous supply or the endogenous secretion is high, the diuretic causes a large excretion of potassium. This can be counteracted by the administration of an aldosterone antagonist.

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AN ALDOSTERONE ANTAGONIST AND DIURETICS IN THE TREATMENT OF CHRONIC ŒDEMA AND ASCITES

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A SERIOUS disadvantage of chlorothiazide treatment is that in some patients it causes potassium depletion and hypokalæmia (Bayliss et al. 1958, Read et al. 1958). This was at first attributed to its inhibiting carbonic anhydrase (Pitts et al. 1958). However, another benzothiadiazine compound, hydroflumethiazide, was also found to produce hypokalæmia, in dosages which did not increase bicarbonate excretion (Edmonds and Wilson 1959). Some other explanation was therefore necessary. Edmonds and Wilson (1960) found that in normal subjects, the proportions of sodium and potassium excreted during a diuresis produced by hydroflumethiazide were determined by the endogenous secretion of salt-retaining hormone and could be greatly altered by administering either excess hormone or an aldosterone antagonist. In many clinical states in which there is retention of salt and water, aldosterone excretion is increased (Farrell 1958), and it seemed possible that the excessive potassium loss sometimes occurring with diuretics was related to this factor. The availability of an effective antagonist of aldosterone has enabled us to test this hypothesis and assess the therapeutic value of this antagonist.

The steroidal spirolactones are a group of compounds synthesised by Kagawa and his associates (1957) which

are closely related in structure to aldosterone. The earlier compounds had to be given by frequent injection, and this, together with their scarcity, has precluded a full clinical trial, although there is evidence of their potential value in certain conditions (Kerr et al. 1958, Liddle 1958, Slater et al. 1959). The spirolactone used in this study, SC-9420 (Searle) has the advantage of being readily absorbed when given by mouth. Studies in normal subjects (Edmonds and Wilson 1960) support the view that its effect on electrolyte excretion, like that of the other steroidal spirolactones (Liddle 1958, Ross and Bethune 1959), is due to its antagonising the action of aldosterone on the renal tubular cells.

The present work describes the various types of response encountered when standard doses of hydroflumethiazide, mersalyl, and spirolactone were given, separately or together, to patients with chronic salt and water retention who required long-term diuretic therapy.

Methods

15 patients were studied. They had all been treated for some months or years with mersalyl, oral diuretics, katonium, or dietary salt restriction to prevent accumulation of œdema or ascites. 2 were on a low-salt diet (about 1 g. sodium chloride daily) during part of the study. The remainder took a normal diet without added salt (about 5 to 8 g. of sodium chloride daily), and fluid intake was unrestricted.

The urine was collected over twenty-four-hour periods starting at 10 A.M. each day. Blood was taken weekly for determination of electrolytes and urea and often more frequently.

The drugs used were mersalyl 2 ml. intramuscularly at 10 A.M. and hydroflumethiazide 100 mg. at 10 A.M. The spirolactone was provided in 100 mg. tablets and initially 100 mg. was given four-hourly from 6 A.M. to a total of 400 mg. daily. Subsequently, larger doses were given to those patients who failed to respond to this amount, and in those who had a satisfactory response the dose was varied to find a maintenance level. In the comparative trial of diuretics, days of treatment were alternated with days without treatment.

Urinary sodium and potassium were estimated by flame photometry, chloride by potentiometric titration with silver nitrate (Sanderson 1952), titratable acidity by titration to pH 7·4 with 0·1*N* sodium hydroxide and ammonia colorimetrically after nesslerisation. Serum electrolytes and urea were determined by routine laboratory methods. Serum and urine creatinine were estimated by the method of Owen et al. (1954).

Results

Response to Hydroflumethiazide

According to their response to hydroflumethiazide the patients have been divided into three groups (table I).

TABLE I—EFFECT OF HYDROFLUMETHIAZIDE, MERSALYL AND THE SPIROLACTONE, SC-9420, ON SODIUM, POTASSIUM, AND CHLORIDE EXCRETION IN PATIENTS WITH CHRONIC ŒDEMA AND ASCITES. EXCEPT WHERE OTHERWISE STATED, THE PATIENTS WERE RECEIVING A NORMAL DIET WITHOUT ADDED SALT (5–8 G. SODIUM CHLORIDE DAILY)

Case	Age and sex	Diagnosis	Urine (mEq. per 24 hours)						
				Untreated Mean of 8 days	Hydroflumethiazide 100 mg.	SC-9420 400 mg.	Hydroflumethiazide 100 mg. and SC-9420 400 mg.	Mersalyl 2 ml.	Mersalyl 2 ml. and hydroflumethiazide 100 mg.
Group 1									
1	F 71	Ischæmic heart-disease	Na	24	102	10	95	115	218
			K	24	29	15	28	36	43
			Cl	29	114	7	111	135	242
2	M 54	Ischæmic heart-disease	Na	112	200	97	220	278	475
			K	77	64	66	64	64	54
			Cl	114	204	88	209	263	485
3	M 56	Hypertensive heart-disease	Na	77	152	91	195	176	227
			K	58	42	62	44	54	67
			Cl	80	174	92	214	153	257
4	M 70	Hypertensive heart-disease	Na	77	242	102	248	235	265
			K	49	60	48	36	29	96
			Cl	69	276	96	241	278	309
5	F 78	Chronic œdema—unknown cause	Na	38	204	31	240	205	331
			K	32	47	29	52	46	33
			Cl	28	215	33	238	215	389
6	F 57	Thyrotoxic heart-disease	Na	26	178	15	232	232	366
			K	19	37	11	45	17	37
			Cl	14	168	13	232	226	384
7	F 66	Chronic rheumatic heart-disease	Na	73	315	148	255	270	396
			K	55	77	52	61	70	90
			Cl	74	354	122	260	290	475
8	F 32	Chronic rheumatic heart-disease	Na	41	204	..	..	209	246
			K	35	58	..	..	52	44
			Cl	38	221	..	..	215	260
Group 2									
9	F 27	Chronic rheumatic heart-disease	Na	6	32	2	55	173	333
			K	18	44	21	18	50	49
			Cl	7	66	5	57	219	376
10	F 46	Chronic rheumatic heart-disease	Na	63	109	126	203	295	476
			K	21	89	39	29	19	73
			Cl	72	140	108	187	270	480
11	F 36	Chronic rheumatic heart-disease: (i) While on katonium 60 g./day	Na	3	18	4	6	28	143
			K	6	18	4	11	18	61
			Cl	41	108	54	97	100	304
		(ii) While on low-salt diet	Na	3	3	8	50	..	106
			K	15	32	20	22	..	39
			Cl	9	23	8	43	..	109
12	F 32	Hepatic cirrhosis (on katonium 60 g./daily)	Na	41	248	108	262	176	297
			K	48	95	56	34	91	272
			Cl	66	331	88	299	234	476
13	F 26	Hepatic cirrhosis with ascites on low-salt diet	Na	7	5	18	200	47	186
			K	85	187	49	123	106	186
			Cl	24	158	8	288	126	362
Group 3									
14	M 32	Chronic rheumatic heart-disease	Na	1	1	..	..	2·5	..
			K	40	33	..	..	33	..
			Cl	12	11	..	..	19	..
15	M 69	Chronic rheumatic heart-disease	Na	6	5	7	6	29	75
			K	55	40	53	66	33	64
			Cl	14	14	7	7	44	88

TABLE II—MEAN DAILY EXCRETION OF SODIUM, POTASSIUM, AND CHLORIDE (MEQ.) PRODUCED BY HYDROFLUMETHIAZIDE, MERSALYL, AND SPIROLACTONE USED ALONE AND IN COMBINATION IN PATIENTS OF GROUPS 1 AND 2

—	Untreated	Hydroflumethiazide 100 mg.	SC-9420 400 mg.	Hydroflumethiazide 100 mg. and SC-9420 400 mg.	Mersalyl 2 ml.	Mersalyl 2 ml. and hydroflumethiazide 100 mg.
Group 1						
Na	58	200	72	212	215	315
K	44	52	40	47	46	58
Cl	56	216	64	214	221	350
Group 2						
Na	20	69	44	129	144	256
K	32	77	32	40	57	113
Cl	36	138	45	162	189	351

In *group 1* sodium and chloride excretion rose in equivalent amounts, while potassium excretion showed no alteration or only a small increase (table II). The results in a typical patient (case 2) are shown in fig. 1.

In *group 2* there was a large rise of potassium excretion with a substantial rise of urinary chloride. The increase in urinary sodium was only slight or moderate. Only one patient (case 10) had fluid retention controllable with hydroflumethiazide alone, and even she required injections of mersalyl occasionally and potassium chloride 3 g. daily (fig. 2). The other patients had previously been found resistant to oral diuretics and this investigation showed that the reason lay in their failure to lose sodium when chloride excretion increased. Moreover, they often developed hypokalæmia within a few days of treatment with oral diuretics (fig. 3). The excretion of potassium on the untreated days was low in this group compared with group 1 (table II). This was probably due to prolonged diuretic therapy which had caused some degree of potassium depletion. Potassium therefore tended to be retained when diuretics were omitted.

One patient (case 11) was mildly acidotic, and her urine on untreated days contained much ammonium and chloride but very little sodium or potassium, these effects being attributable to the katonium she was receiving at that time (fig. 4). When hydroflumethiazide was given, there was a moderate increase in chloride excretion, but this was accompanied principally by ammonium ions: sodium and potassium excretion were only slightly increased.

Finally, 2 cases have been separated into *group 3*. They were distinguished by failing to show any change in electrolyte excretion with hydroflumethiazide.

Response to SC-9420

7 patients in group 1 were treated with spirolactone. In 5, doses of 400 and 800 mg. had no effect on urine volume and composition. 2 cases (4 and 7) showed a moderate elevation of sodium and chloride excretion, although the effect was very much less than that of hydroflumethiazide. Potassium excretion was not significantly changed in any of the patients.

2 patients in group 2 (cases 10 and 12) had a significant rise of sodium and chloride excretion when the spirolactone was given alone; potassium excretion was little altered. The action of the drug often persisted to some extent on the following day (fig. 2).

It was possible to use the spirolactone on only 1 of the cases in group 3, and in this patient, even in doses of up to 800 mg. daily for several days, it had no significant effect.

Response to Hydroflumethiazide plus SC-9420

In patients of group 1 when hydroflumethiazide was given with spirolactone electrolyte excretion was much the same as when hydroflumethiazide was given alone. In all patients of group 2, however, the response to hydroflumethiazide was considerably modified when SC-9420 was given simultaneously. Chloride excretion was little greater (except for some increase in case 13), but the excretion of potassium was greatly reduced and of sodium increased, resulting in a satisfactory sodium and chloride loss (figs. 2 and 3). The considerable increase of ammonium excretion which accompanied the chloride loss induced by hydroflumethiazide in case 11 was unaffected by concurrent administration of spirolactone (table I) even in doses as high as 1200 mg. daily.

No effect was observed in the one patient of group 3 in whom the action of the combination of drugs could be examined.

Response to Mersalyl

Chloride excretion was increased by mersalyl in all patients.

In group 1 sodium and chloride were excreted in nearly equal amounts and potassium excretion was unchanged. In group 2 urinary potassium rose substantially in cases 9 and 12, rose slightly in cases 11 and 13, and in case 10 was unchanged. When case 11 was on katonium, mersalyl, like hydroflumethia-

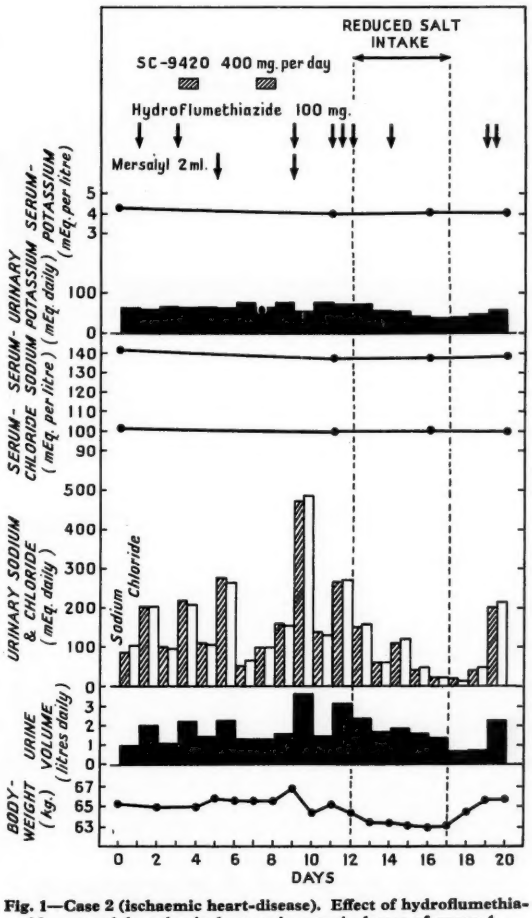

Fig. 1—Case 2 (ischaemic heart-disease). Effect of hydroflumethiazide, mersalyl, and spirolactone in a typical case of group 1.
Hydroflumethiazide increased sodium and chloride excretion but potassium excretion was unaffected. The spirolactone was without effect. During the five days he was taking a reduced salt intake (about 50 mEq. sodium daily), his weight fell and his œdema disappeared completely. When salt intake was restored to its usual level, his weight rose rapidly and œdema reappeared.

zide, produced a rise of chloride excretion but this was chiefly associated with ammonium ion, and sodium and potassium excretion were only moderately increased (fig. 4). A similar phenomenon was observed in case 13 when this patient was receiving katonium (fig. 3).

Case 14 in group 3 showed little alteration in urinary electrolytes with mersalyl, but in case 15 there was a moderate increase in sodium and chloride excretion.

Response to Hydroflumethiazide plus Mersalyl

All patients in whom this combination was examined had a considerable rise of sodium and chloride excretion.

In group 1 potassium excretion was little altered; but in all patients of group 2 it showed a large increase. Of group 3, the combination was tried only in case 15, and it produced a substantial rise of urinary sodium and chloride, with a small increase of urinary potassium excretion.

Comparison of Mersalyl and Hydroflumethiazide

Table II shows that in most cases mersalyl 2 ml. and hydroflumethiazide 100 mg. caused about the same increase in chloride excretion, although occasionally (e.g., cases 9 and 10) the increase with mersalyl was much greater (table I).

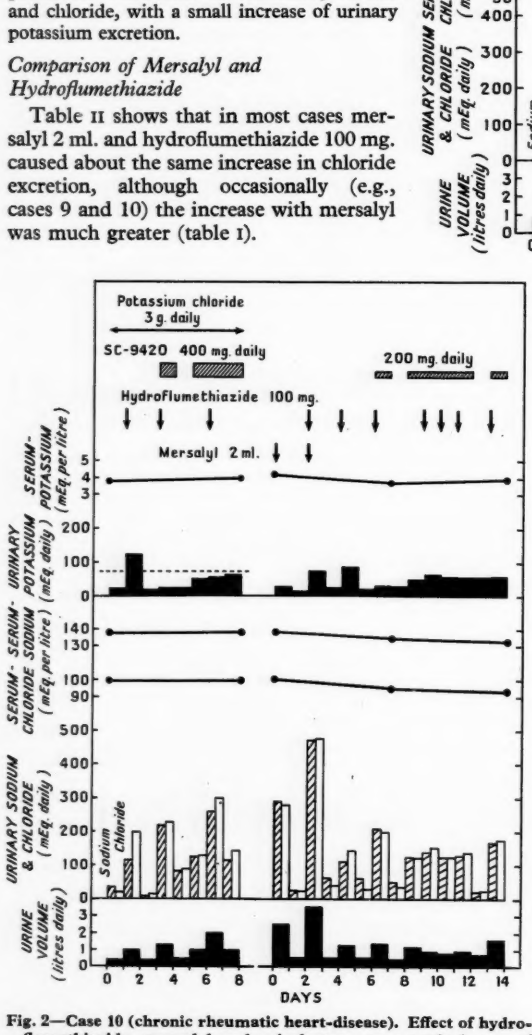

Fig. 2—Case 10 (chronic rheumatic heart-disease). Effect of hydroflumethiazide, mersalyl and spirolactone on a typical case of group 2.

The horizontal dotted line during the first study indicates the level of potassium intake.

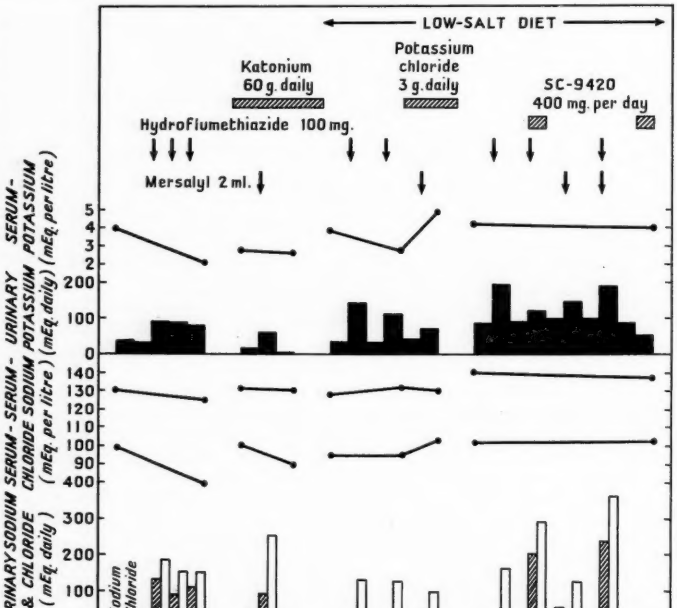

Fig. 3—Case 13 (hepatic cirrhosis and ascites).

When this patient was on a normal diet, hydroflumethiazide increased sodium, potassium and chloride excretion and lowered the serum-potassium level; but ascites formation continued. While receiving katonium, she responded to mersalyl by a rise of urinary sodium, potassium, and ammonium to accompany the increased chloride excretion. On a low-salt diet, hydroflumethiazide increased excretion of potassium and chloride but not of sodium. Spirolactone, given in addition, reversed this phenomenon.

In group 1 neither mersalyl nor hydroflumethiazide caused much increase of potassium excretion, but in group 2 both tended to raise urinary potassium. While it appeared, therefore, that the effect on potassium excretion depended more on the patient's state than on the diuretic employed, there was some difference between the two drugs in this respect. Compared with hydroflumethiazide, mersalyl produced a greater rise of sodium and a lesser rise of potassium in the same patients (table II).

In the majority of patients, when hydroflumethiazide and mersalyl were given together the increase of chloride excretion was approximately equal to the sum of the increases when they were given independently (table II). In several patients of group 2, however, and in case 15 of group 3, the effect was one of potentiation, chloride excretion being increased much more than would be expected by mere addition of responses. In one patient (case 11) while on katonium, the excretion pattern was substantially altered by administering the drugs together, a much larger proportion of sodium and potassium accompanying chloride (fig. 4).

During the hydroflumethiazide diuresis the concentration of chloride in the urine was $109 \pm 7{\cdot}8$ (S.E.) mEq. per litre (mean of 13 observations) and during the mersalyl diuresis it was $105 \pm 7{\cdot}8$ mEq. per litre (mean of 13 observations). This difference was not significant. When

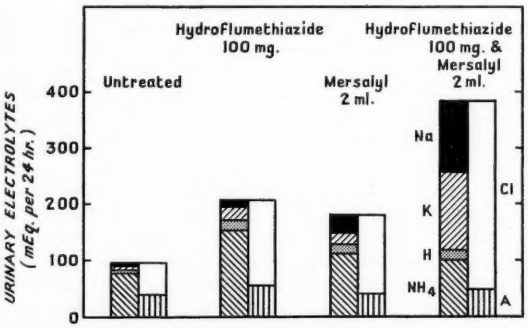

Fig. 4—Case 11 (chronic rheumatic heart-disease). Effect of hydroflumethiazide and mersalyl on a patient taking katonium 60 g. daily.

The increase of chloride excretion produced by the diuretics given independently was accompanied chiefly by ammonium ions. A= undetermined anion.

mersalyl and hydroflumethiazide were given together, the urinary chloride concentration was higher at 131±4·9 mEq. per litre (mean of 13 observations); a difference which was significant ($P < 0.01$).

Comparison of Groups 1 and 2

The striking differences between these groups as regards potassium excretion and the action of spirolactone have already been described; but in addition other differences were observed.

The rate of sodium excretion on the untreated days was generally distinctly lower in group 2 than in group 1.

The increase of chloride and cation excretion produced by mersalyl and hydroflumethiazide given independently was lower in group 2 than in group 1; but, when they were given together, chloride excretion increased to a similar extent in the two groups.

Serum electrolytes and urea showed no significant difference between the groups. Creatinine clearance did, however, show a difference; the mean value for the patients of group 1 was 70±5·2 (S.E.) ml. per min. and for those of group 2 was 49±5·8 ml. This difference was significant ($P < 0.01$). The creatinine clearance in the two patients of group 3 was very low, being 33 ml. per min. in case 14 and 21 ml. per min. in case 15.

Liver function, as shown by serum bilirubin and flocculation tests, was abnormal in most of the patients of this series. These disturbances could not be correlated with the groups. A clinical observation which may be significant was that all the patients of group 2, when deprived of diuretic therapy, developed ascites as the earliest sign of fluid retention, whereas those of group 1 developed œdema first and ascites later.

Maintenance Therapy

The results indicated that a combination of hydroflumethiazide and spirolactone, or possibly spirolactone alone in some cases, would control fluid retention in patients of group 2 who could not be treated with hydroflumethiazide alone. Table III summarises the present treatment of patients of group 2 and shows how effective this therapy can be in suitable cases. Mersalyl injections, katonium, and rigid salt restriction have been eliminated in patients who had been subjected to them for many months or years. In some cases, however, limitation of salt intake is still necessary, and this depends on the extent to which sodium and chloride excretion can be increased by the therapy. In case 11, for example, where the response to very large doses of hydroflumethiazide and spirolactone was small, salt intake has had to be restricted to 3–4 g. daily. This patient is the most advanced case of group 2, and even when treated with katonium and mersalyl injections, she tended gradually to accumulate ascites. The principal improvement in her case has come from the elimination of the injections and the katonium.

One patient (case 10) on one occasion and for no obvious reason, developed resistance to combined therapy. As the patient was collecting urine specimens at the time, it was possible to follow the changes. Urinary volume and sodium and chloride excretion fell, potassium excretion being unchanged. Œdema and ascites developed rapidly. After a few days' rest in bed in hospital, the action of the drugs was restored and the combined therapy has since remained satisfactory. This patient, in fact, was temporarily transferred from group 2 to group 3, but the situation was redeemed by rest.

Side-effects of Spirolactone

No side-effects have been encountered with SC-9420, even when doses as high as 1200 mg. daily were used. None of the patients or normal subjects have complained of digestive disturbances; no rashes have been associated with the treatment; and there have been no changes in hæmoglobin or white-cell count and no albuminuria or other urinary abnormality.

Discussion

The mercurial and benzothiadiazine diuretics are similar in their effects on the composition of the urine, producing an increase of chloride excretion accompanied by sodium and a varying quantity of potassium, hydrogen, and ammonium ions. Nevertheless, the results presented here show that definite differences exist, and they are in

TABLE III—COMPARISON OF PREVIOUS AND PRESENT DIURETIC TREATMENT OF PATIENTS OF GROUP 2

Case	Previous treatment		Present treatment		Comment
	Diet	Drugs	Diet	Drugs	
9	Normal	Mersalyl 2 ml. three times weekly	Normal	Spirolactone 100 mg. t.d.s. Hydroflumethiazide 100 mg. daily	Improved
10	Normal	Hydroflumethiazide 100 mg. daily Potassium chloride 3 g. daily Mersalyl 2 ml. occasionally	Normal	Spirolactone 100 mg. b.d. Hydroflumethiazide 100 mg. twice weekly	Improved
11	Normal	Mersalyl 2 ml. three times weekly Katonium 60 g. daily	Salt restricted to 3 g. daily	Spirolactone 100 mg. t.d.s. Hydroflumethiazide 100 mg. daily	Unchanged
12	Normal	Mersalyl 2 ml. three times weekly Katonium 60 g. daily	Normal	Spirolactone 100 mg. t.d.s. three times weekly Hydroflumethiazide 100 mg. three times weekly OR Spirolactone 100 mg. t.d.s. on alternate days	Either of these regimes has resulted in great improvement
13	Low salt	Mersalyl 2 ml. three times weekly	Normal	Spirolactone 100 mg. t.d.s. three times weekly Hydroflumethiazide 100 mg. three times weekly OR Spirolactone 100 mg. t.d.s. every day	Either of these regimes has resulted in great improvement

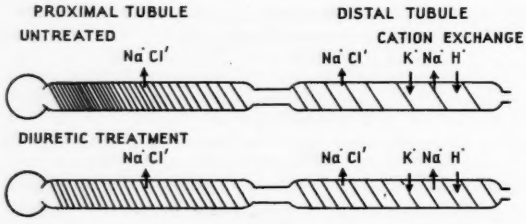

Fig. 5—Hypothetical scheme to explain the increased potassium and hydrogen-ion loss with diuretics.

During the action of the diuretic an increased amount of sodium and chloride reaches the cation-exchange region of the distal renal tubule. The exchange is considerably enhanced by salt-retaining steroids. Sodium and chloride are represented by shading.

agreement with previous findings in dogs (Pitts et al. 1958) in suggesting that mercurial and benzothiadiazine diuretics have a basically different action on the sodium and chloride reabsorbing mechanism of the renal tubular cells.

The potassium loss sometimes produced by diuretics attracted little attention until recently (Cort and Matthews 1954, Flear et al. 1958), but the introduction of potent oral diuretics has brought it into prominence. My findings suggest that mersalyl and hydroflumethiazide increase potassium excretion in the same type of patient. Although the increase is commonly greater with hydroflumethiazide —perhaps because the mercurials also depress potassium secretion (Berliner et al. 1951)—mersalyl can cause considerable potassium loss in some patients. Probably the association of hypokalæmia with oral diuretics is partly due to their being given daily, whereas mersalyl is usually given only three times a week. Treatment on alternate days allows the kidney to retain potassium on the days when no treatment is given, and thus make up for the loss (fig. 2).

The effects on potassium excretion can be explained if the diuretics act at a site proximal to the renal tubular region where the sodium-potassium exchange occurs, and there is experimental evidence that they do (Vander et al. 1958, 1959). As a consequence, sodium chloride is presented to the cation-exchange region in larger quantities (fig. 5), and when this mechanism is under stimulation by endogenous or exogenous salt-retaining steroids, excessive exchange occurs leading to a great urinary loss of potassium (Edmonds and Wilson 1960). The present results give no indication whether these diuretics act primarily by inhibiting reabsorption of sodium or chloride, since the final composition of the urine must depend on cation exchange in the distal tubules.

In 2 cases (11 and 13), when mersalyl or hydroflumethiazide was given while the patients were taking katonium, the substantial rise of chloride excretion was mainly accompanied by ammonium ions. Consequently, although urine volume was considerably increased, the diuretics were not producing a satisfactory result. Again, the explanation is probably in terms of an exchange in the distal renal tubules; on this occasion, hydrogen ions instead of potassium ions exchanged with sodium, and ammonia produced by the renal tubular cells diffused into the lumen to combine with the hydrogen ions. As both patients had some degree of acidosis resulting from administration of katonium, hydrogen ions were freely available for exchange with sodium. A similar phenomenon can be demonstrated in acidotic salt-depleted rats (Edmonds 1960): acidosis appears to be the essential requirement. When the same patients were no longer taking katonium, the action on ammonia excretion disappeared and the increase of chloride excretion was balanced by an increase of sodium and potassium excretion (table I and fig. 3).

The alteration of the excretion pattern in case 11 when mersalyl and hydroflumethiazide were given together was probably due to sodium and chloride being presented to the exchange region in such quantities that the renal tubular capacity for ammonia production was exceeded. The result was that much of the sodium was not reabsorbed and some was exchanged for potassium.

The object of diuretic therapy is to enable the daily salt intake to be excreted and to reduce the volume of extracellular fluid to a normal level. Consequently, the ideal diuretic induces loss of sodium and chloride in nearly equivalent amounts. In patients in whom hydroflumethiazide had this effect (group 1), it provided satisfactory therapy. The remaining patients, however, were partially or completely resistant, and this resistance proved to be of two types.

One type was characterised by an increase of chloride excretion, which was, however, accompanied by the wrong cations—generally potassium instead of sodium (group 2). Here the diuretic increased urine volume yet failed to control the formation of œdema or ascites; and the patients ran the further risk of rapid potassium depletion. Evidently, therefore, excretion of chloride was a guide to the activity of the diuretic but not necessarily to its therapeutic value. In patients with resistance of this type, the spirolactone restored the efficacy of the diuretic —probably by blocking the action of salt-retaining steroids and thereby reducing the sodium-potassium exchange in the distal renal tubules.

In the other type of resistance to diuretics, chloride excretion was not increased by hydroflumethiazide, and the effect of mersalyl was also poor (group 3). Probably the considerable reduction in glomerular filtration rate was an important factor in their resistance but sometimes this did not seem to be the explanation. Case 10, for example, behaved temporarily like this group, although serum electrolytes and urea were normal.

There is no obvious reason why the salt-retaining steroid activity of some patients seemed to be high while in others it was low. Diuretics and low-salt diet may increase aldosterone production, but all the patients of this study had received diuretics for a considerable period, and although 3 of those in group 2 had their dietary salt severely restricted, 2 were on a normal diet. 2 of the patients of group 2 had ascites and hepatic cirrhosis—a condition often associated with increased excretion of aldosterone (Wolff et al. 1958).

To ascertain the type of diuretic response is of practical importance for the therapeutic use of the spirolactone. This drug is of great value in cases where oral diuretics of the hydroflumethiazide type cause a rise of chloride excretion accompanied by a considerable rise of potassium excretion. As our supplies of the spirolactone were limited, most attention was paid to combined treatment with a diuretic and spirolactone. This has been very satisfactory in suitable cases; but preliminary studies have shown that some patients, particularly those with hepatic cirrhosis and ascites without heart-disease, can be successfully treated with the steroidal lactone alone.

Summary

The action of a typical benzothiadiazine diuretic (hydroflumethiazide), of mersalyl, and of a steroidal spirolactone (SC-9420) has been examined in a group of patients with chronic œdema or ascites. The responses fell into three main types:

Group 1.—Both hydroflumethiazide and mersalyl produced a large rise of sodium and chloride excretion with little or no change in potassium excretion. Spirolactone had little action in these cases.

Group 2.—Hydroflumethiazide produced a rise of chloride excretion associated with increased potassium excretion; sodium excretion rose in some cases but in others it barely altered. Mersalyl had a similar effect but the proportion of sodium to potassium excreted was larger than with hydroflumethiazide. Spirolactone by itself increased sodium excretion in some of these cases; and, when given with hydroflumethiazide, it always greatly reduced the amount of potassium and increased that of sodium accompanying the chloride.

Group 3.—Hydroflumethiazide did not affect electrolyte excretion and mersalyl caused only a slight increase of urinary sodium and chloride; potassium excretion was unaffected. Spirolactone had no effect.

In the majority of cases mersalyl 2 ml. was approximately equivalent to hydroflumethiazide 100 mg. but in some cases mersalyl had a much greater effect.

When mersalyl and hydroflumethiazide were given together, their actions were usually summated; but in several cases there was considerable potentiation.

In patients taking katonium in dosage sufficient to produce a mild acidosis, mersalyl and hydroflumethiazide caused a considerable rise of chloride excretion, accompanied by ammonium, with little effect on sodium and potassium excretion.

The spirolactone, SC-9420, is of considerable value in patients of group 2 who are resistant to benzothiadiazine diuretics—and to a lesser extent mersalyl—because they lose potassium instead of sodium with the increased excretion of chloride. This effect, which is probably attributable to excessive salt-retaining steroid activity, can be reversed by spirolactone. All the patients of this group have been satisfactorily maintained for many weeks on this combined treatment.

I wish to thank Prof. G. M. Wilson for his advice and encouragement; Dr. G. R. Venning, of G. D. Searle and Co. Ltd., for supplies of SC-9420 (' Aldactone '); and Dr. E. V. Morton, of Boots Pure Drug Co. Ltd., for supplies of hydroflumethiazide.

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BRONCHOGRAPHY

A NEGLECTED INVESTIGATION ?

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THERE seems to be a general impression in Britain that bronchography is a difficult technique of limited value. At a recent symposium on disordered pulmonary function one speaker stressed its difficulties, and suggested that a lengthy procedure of posturing and preferably selective bronchial catheterisation were necessary to obtain good bronchograms.

In this hospital a contrary view is held. The procedure need be neither difficult nor time-consuming.

Important diagnostic information can readily be obtained by bronchography alone or as a complement to bronchoscopy. It is our common experience that bronchography will yield vital information especially in bronchial neoplasm, primary and chronic tuberculosis, and bronchiectasis when other methods of investigation have yielded negative results.

This paper briefly describes the technique used with success at Sully Hospital in the past ten years. The trachea is intubated by direct laryngoscopy. From January, 1950, to December, 1959, 5098 bronchograms were done (465 in 1959). The great majority were technically satisfactory, and there were very few failures at the first attempt. The technique is quite easy to master. New house-physicians do many of the routine bronchograms within a few weeks of arriving at the hospital. The method is readily applicable to outpatients, who are allowed home on the same day. Bilateral bronchography, if indicated, is routinely done at one session. Patient acceptance is very good—largely owing to the rapidity of the method and the completion of the investigation at one session.

After a little experience with the laryngoscope a patient is seldom caused much discomfort. No serious side-effects

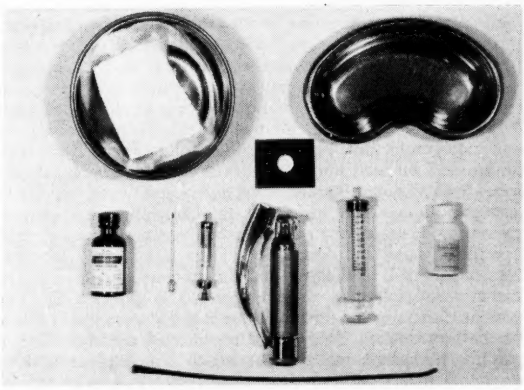

Fig. 1—Materials for bronchography.

have occurred, although some patients have slight pyrexia and malaise for a day or two afterwards.

It is not proposed to discuss other methods which are well known; nor is it claimed that our method is necessarily the best. As with all other techniques, teamwork, practice, and experience play an important part. We merely reiterate that our technique has proved rapid, easy, and very informative. We suggest that it should be used more widely not only in chest units but in general hospitals, where bronchography sometimes tends to be a rather major undertaking.

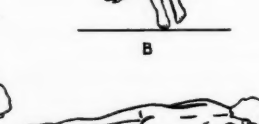

Fig. 2—Positions for bilateral bronchography.

Technique

Fig. 1 shows the necessary materials for bronchography. 'Dionosil Aqueous' (Glaxo) (50% aqueous suspension of propyliodone) and the gum-elastic catheters are normally kept on ice until just before their use.

1. Half an hour before intubation the adult patient of average size is premedicated with 'Omnopon' gr. $^1/_6$ and scopolomine gr. $^1/_{150}$. Twenty minutes later he is instructed to suck a lozenge containing gr. 1 of amethocaine. Since 1945 this lozenge has been made in the hospital pharmacy (see appendix), and many observers have confirmed that it produces more complete surface anæsthesia of the oropharynx than the usual proprietary brands—probably because it dissolves more slowly than proprietary preparations. At least five minutes of constant sucking are necessary to dissolve the lozenge, which gradually wears down to a very thin sliver.

2. The patient lies on his back on the X-ray table with a soft pillow under his head. A Macintosh laryngoscope is passed over the back of the tongue and in front of the epiglottis. By lifting the tongue forwards the vocal cords are exposed. Occasionally, if the epiglottis is very long the instrument may have to be passed behind it.

3. A gum-elastic catheter 13 in. long, with a slight bend at its tip, and fitted at its other end with a metal adaptor for a 'Record' syringe, is then introduced into the pharynx and passed well down between the cords on inspiration.

4. The laryngoscope is withdrawn, the patient sits up and 2 ml. of 4% lignocaine ('Xylocaine') are immediately injected via the catheter. As the patient coughs, the surface anæsthetic is distributed throughout the bronchial tree.

5. The catheter is brought to the right angle of the mouth and secured to the patient's right cheek with adhesive plaster about 2 in. from its end.

6. When both sides are to be filled the right side is filled first. A physiotherapist carefully supports the patient in each position (fig. 2) for about 10 seconds after the medium has been injected. Adequate support is important to avoid strain and consequent coughing. The patient should not of course be allowed to bend over to the other side until filling of one side has been completed and radiographs have been taken. 20 ml. of dionosil aqueous are used to fill each lung. To fill the right middle and lower lobes 5 ml. of dionosil are injected fairly rapidly and steadily in each of positions A, B, and C (fig. 2). Coughing can usually be prevented by asking the patient to hold his breath and then to breathe through the nose. To fill the right upper lobe the remaining 5 ml. of dionosil and the amount contained in the catheter (by injecting air) are injected in position D. The patient is then moved into positions E and F to complete filling of the upper lobe. The patient remains on the right side in position F, and a lateral film is taken in held inspiration. The patient is then moved into the supine position and an anteroposterior film is taken. The catheter is withdrawn 1 in. and moved to the left angle of the mouth, thus ensuring that the tip lies free of the right main bronchus. The left bronchial tree is filled in essentially the same way as the right except that the lingula is filled with the patient in position G, which thus takes the place of position C. Anteroposterior and left posterior oblique films are then taken. Details of the radiographic technique for an average adult are given in the appendix.

7. The catheter is removed and the patient encouraged to cough vigorously. He is then returned to the ward lying on his side for ease of coughing. If only one side has been filled he should lie on the opposite side. He is encouraged to cough during the next few hours and most of the dionosil is expectorated. He is not allowed to eat or drink for two hours after bronchography, by which time most of the anæsthesia has passed off and danger of aspiration is slight.

An important part of bronchography is the careful positioning of the patient. A trained assistant is necessary to position and support the patient; in Sully Hospital the assistant normally is a physiotherapist.

We believe that a fairly rapid, steady injection helps to ensure good filling. It seems likely that a bolus of medium will spill into adjacent segmental and subsegmental bronchi, whereas slow injection will fill only the dependent bronchi.

With a little practice bilateral bronchography can readily be performed within 15 minutes of the patient being placed on the X-ray table. It is therefore quite possible to perform five or six bronchographies in a two-hour session.

The same technique is used for post-bronchoscopy bronchograms, the catheter being inserted by the bronchoscopist on completion of bronchoscopy. Patients tolerate the combined procedure well. Although the quality of the bronchograms tends to be less good than with the primary procedure, important information has frequently been obtained in cases where bronchoscopy has been negative—notably through the demonstration of segmental or subsegmental blocks due to neoplasm.

Premedication

Large or very nervous patients may require up to gr. $^1/_3$ omnopon. Promezathine ('Phenergan') 25 mg. intramuscularly has been found effective and safe in old and emphysematous subjects, in whom dangerous respiratory depression may follow the use of even small doses of omnopon. Intramuscular chlorpromazine ('Largactil') has also been used in such patients, but in 1 patient

caused considerable skin necrosis at the site of the injection, because this was not given deeply into the muscle.

Children under the age of 12 years are normally given a general anæsthetic. Otherwise the procedure is essentially the same as in adults. A child of 5 years will usually receive about 8 ml. of dionosil on each side.

Despite the experience of others we have not found dionosil aqueous unduly irritating with the above anæsthetic regime. We find that it provides better contrast and more rapid clearing than the oily suspension of dionosil. With dionosil aqueous, should coughing occur, excessive alveolar filling is unusual, in this respect it is much superior to iodised oil.

We are very grateful to Dr. H. M. Foreman and Dr. L. R. West for helpful advice and permission to publish this paper. We thank Dr. J. C. Meek and Mr. W. Davey for help with radiographic aspects. We are particularly indebted to Miss Verna Davies, M.C.S.P., and the many physiotherapists whose expert assistance and enthusiasm have contributed so much to the success of the method. Miss Davies provided the drawings and made many valuable suggestions during the preparation of this paper.

Appendix

METHOD OF PREPARATION OF AMETHOCAINE LOZENGES

Amethocaine hydrochloride	gr. 160
Sucrose (icing-sugar)	gr. 212·5
Pulv. acacia	gr. 160
Tinct tolu	80 minims
Aq. dest.	Q.S.

The acacia and amethocaine powder are mixed and small portions of icing-sugar are added. The tincture of tolu and water are added to prepare a mass sufficiently plastic to be rolled and cut without crumbling. The mass is weighed, rolled, and divided into lozenges containing amethocaine gr. 1. These are then dried at 40°C for 24 hours.

RADIOGRAPHIC TECHNIQUE FOR BILATERAL BRONCHOGRAPHY IN AN AVERAGE ADULT

1. Right lateral	85 kV	400 mA	0·08 sec.
2. Right anteroposterior	70 kV	400 mA	0·06 sec.
3. Left anteroposterior (to include right side)	75 kV	400 mA	0·06 sec.
4. Left posterior-oblique	75 kV	400 mA	0·06 sec.

All films are taken at a tube-film distance of 40 in. The patient is supine or lies on the side.

LOCAL TREATMENT OF ULCERATIVE COLITIS WITH PREDNISOLONE-21-PHOSPHATE ENEMATA

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LOCAL methods of therapy for ulcerative colitis or ulcerative proctosigmoiditis have been tried unsuccessfully for many years. In 1956 Truelove described a method of intrarectal infusion of an alcoholic solution of hydrocortisone by means of a drip-set and rubber catheter. This gave very satisfactory results and was improved when an aqueous solution of hydrocortisone hemisuccinate was used in the same way (Truelove 1957).

In an endeavour to simplify local methods of administration of corticoids it was decided to investigate the effect of a solution of a soluble prednisolone derivative—prednisolone-21-phosphate (Glaxo)—given as a small retention enema, using a disposable plastic bag (figs. 1 and 2).

Preliminary Trial

In order to test whether a solution given as a small-volume retention enema would reach much of the colon, a preliminary trial was carried out in which 100 ml. of 40% suspension of barium was put in the plastic bag and introduced into the rectum in the same way as the therapeutic enemata were to be given. X-ray films were taken after a few minutes to determine how far the radio-opaque solution had reached. These tests were carried out in patients with ulcerative colitis, and an average example of the resultant film is shown in fig. 3. This reveals that a solution so introduced goes a long way into the colon. The importance of the patient rolling on to the abdomen after the enema was revealed by watching the progress of the solution on the screen between taking films (Matts and Gaskell 1960).

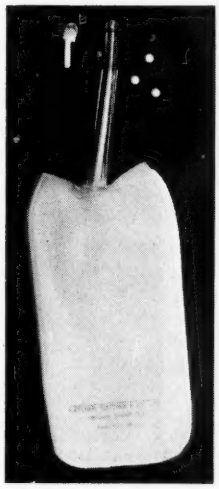

Fig. 1—Disposable plastic bag for enema.

Having thus established that the enema could effectively reach much of the distal colon, a " double-blind " trial was begun, employing a method of restricted sequential analysis developed by Armitage (Snell and Armitage 1957, Watkinson 1958).

A " double-blind " trial was considered necessary because both the prednisolone-21-phosphate solution and the method of administration are new and untried. Any new therapy is liable to exert a powerful suggestive effect and results are therefore subject to observer bias.

Method

Patients in pairs were allocated to either " potent " or " inert control " treatment according to a system of random numbers. The code was not revealed to the physicians until treatment and assessment were complete.

Fig. 2—Self-administration of enema.

The advantage of sequential analysis is that the trial can be stopped as soon as a predetermined boundary of significance has been attained. The design used in this trial is the same as that used by Watkinson (1958), and requires a maximum of 13 united pairs (i.e., perhaps more than 26 patients). If the contrast is sufficiently striking the trial may stop after 6, 11, or 13 untied pairs have been observed. As it happened, it was possible to stop this trial at 12 patients (6 untied pairs) because the appropriate boundary on the chart had been reached.

Therapy

All patients were given twenty-eight days' supply of treatment, consisting of twenty-eight enema bags filled with normal saline solution (approximately 100 ml.) and twenty-nine solution tablets (one spare to allow for accidents), the tablets

Fig. 3—Radiograph showing radio-opaque solution introduced by enema.

being identical for inert and potent preparation. The potent preparation was a solution tablet containing the equivalent of 20 mg. of prednisolone in the form of the 21-phosphate. The patients were instructed as follows:

Every night, when preparing for bed, take out one solution tablet and one filled enema bag. Remove the stopper from the bag and drop the solution tablet down the nozzle into the saline. Replace the stopper, shake the bag, and put it down for ten to fifteen minutes while finishing preparations for bed. When ready, go to bed and lie on the left side with knees drawn up. Reshake the bag, then remove the stopper and lubricate the nozzle with 'Vaseline'. Gently insert the nozzle into the rectum. Slowly roll up the bag like a tube of toothpaste, and the solution will thus be gradually (in one to two minutes) introduced into the rectum. (The purpose of rolling the bag is to prevent regurgitation of the fluid into the bag should the pressure be accidentally released.) When all the solution has been introduced, remove and discard the bag. Roll over on to the abdomen for three to five minutes and then go to sleep in any comfortable position. The treatment is to be carried out nightly.

Assessment

Four possible gradings were used: (1) great improvement, (2) slight improvement, (3) no improvement, (4) worse.

Grading was decided by comparison of the following four main points (in each case before therapy and at the end of therapy): (*a*) general feeling and symptoms (i.e., number of stools daily, presence of fresh blood or mucus, presence or absence of abdominal pain, tenesmus, &c.); (*b*) sigmoidoscopic findings, which were fully recorded and compared; (*c*) haemoglobin and erythrocyte-sedimentation rate (E.S.R.); (*d*) rectal biopsy, which was carried out before and after therapy. These comparisons resulted in a clear-cut distinction in most cases, but where there was any doubt an independent referee (Dr. J. M. Naish) was available.

TABLE I—PATIENTS RECEIVING PREDNISOLONE

Case no.	Age (yr.)	Sex	Pre- and post-treatment assessment								Comment
			Hb (%)	E.S.R.*	Stools daily	Blood	Mucus	Pain	Sigm.†	Biop.‡	
2	46	F	66 69	44 43	2 1	+ −	+ +	+ −	3 2	4 3	Slightly improved
3	40	F	88 91	31 20	1–2 1	+ −	+ −	+ −	3 1	4 2	Greatly improved
6	24	M	96 102	11 8	3–5 1–2	+ −	+ −	+ −	4 2	4 2	Greatly improved
8	48	F	60 64	48 45	6 1–2	+ −	+ −	+ −	4 2	4 3	Greatly improved
11	54	F	90 92	12 10	6 1	+ −	+ −	+ −	3 1	3 2	Greatly improved
12	37	F	98 91	27 28	20 1	+ −	+ −	+ −	4 1	4 2	Greatly improved

*Westergren, uncorrected (mm. in first hour).
†Sigmoidoscopic findings: 1=normal; 2=mild granularity with minimal contact bleeding; 3=marked granularity, contact bleeding, possibly some blood in lumen; 4=severe hæmorrhage and ulceration.
‡Biopsy findings: 1=normal muscoa; 2=minimal infiltration with polymorphs or round cells of mucosa and lamina propria; 3=severe infiltration of mucosa and lamina propria with polymorphs and round cells; 4=mucosal ulceration and severe cellular infiltration.

Selection of Patients

Only patients with undoubted active ulcerative colitis were included. This was, in all cases, diagnosed by the clinical features, by sigmoidoscopy, and by histological changes in a biopsy of specimen of the rectal mucosa. Other lesions in the colon were excluded by barium studies. The patients had not been on any other therapy for at least three months previously, and the prednisolone-21-phosphate enemata were not combined with any other therapy.

No patient whose life was in immediate danger was included in the trial.

Results

Sequential analysis showed a significant result in favour of the potent preparation. The results were plotted on a diagram with boundaries as shown in figs. 2 and 3 of Watkinson (1958). The first six pairs all showed an advantage in favour of the potent preparation, and the appropriate boundary (indicating a significant result in favour of the potent preparation) was then reached (as shown in Watkinson's fig. 2). Of the 6 patients who received prednisolone 5 were greatly improved, and 1 was slightly improved; of the 6 patients who received inert tablets 2 were slightly improved, 1 was unchanged, and 3 were made worse. The detailed results are shown in tables I and II.

TABLE II—CONTROL CASES

Case no.	Age (yr.)	Sex	Pre- and post-treatment assessment								Comment
			Hb (%)	E.S.R.*	Stools daily	Blood	Mucus	Pain	Sigm.†	Biop.‡	
1	30	M	99 100	14 34	3 7	+ +	+ +	+ +	4 4	3 4	Worse
4	23	M	108 96	4 11	2 3	+ +	+ +	+ +	4 4	3 4	Worse
5	55	F	89 81	25 27	3 4	+ +	+ +	+ +	3 4	3 4	Worse
7	53	F	96 93	26 23	1–5 2–4	+ +	+ +	+ −	3 2	4 4	Slightly improved
9	54	F	88 85	21 20	4–5 4	+ +	+ +	− −	3 3	3 3	Not improved
10	48	F	71 80	24 21	8 5	+ +	+ +	+ +	3 2	3 3	Slightly improved

*, †, ‡. See table I.

All patients, after completing the trial and assessment but before the agent used was made known, were put on fourteen days' treatment with known prednisolone-21-phosphate enemata and were then reviewed again. All the patients who had been "slightly improved", "not improved" or "worse", showed great improvement; those who had been "greatly improved" continued to improve. When the agent used in the trial was revealed at the end, these results were scrutinised, and it was found that all the patients who had improved dramatically had done so when changed from the inert to the potent preparation. They had thus acted as their own controls.

Patients were followed up for a further two months, during which none of the group who had been treated with prednisolone-21-phosphate relapsed. Since the "double-blind" trial has been completed, a further 20 patients have been treated with known prednisolone-21-phosphate enemata and 19 have improved greatly.

Discussion

From the results of the "double-blind" trial, reinforced by the results of the therapy with known prednisolone-21-phosphate retention enemata, there would seem to be little doubt that this method of treatment is effective in ulcerative colitis. Whether it is more effective than the drip method using hydrocortisone sodium succinate remains to be seen, but it has three main advantages over the latter method: (1) it is easier, less cumbersome, and less time-consuming for the patient; (2) it is easier to explain and demonstrate, and for the patient to administer, thus saving nurses' and doctors' time; (3) prednisolone-21-phosphate is more stable in an aqueous solution than hydrocortisone hemisuccinate and is potentially cheaper.

Objections which have been raised to this method of enema administration are: (*a*) that the infused fluid will not be retained, (*b*) that it will not reach further than the rectum, (*c*) that the nozzle may damage the rectal wall. In the course of more than 1000 administrations of the enemata there has not been a single patient who has been unable to retain the small quantity (100 ml.) of solution for at least two hours, and almost all the patients retained it for the whole night. The radiographic studies have proved that the solution reaches at least as far as similar quantities administered by the slow-drip method, and no cases of damage to the rectal wall have occurred. The plastic nozzle is soft and pliable and would be unlikely to cause damage even if inserted as far as possible into the rectum; as only half the nozzle is normally inserted damage is even more unlikely. In fact, no snags have been found so far in this method of administration.

Theoretically local prednisolone enemata seem to be particularly suited to cases of ulcerative colitis involving the distal parts of the colon; they may, as I have found, easily be combined with other methods of therapy. The method of preparing the solution freshly for use precludes any possibility of deterioration.

Summary

Local treatment of ulcerative colitis by means of a disposable plastic bag containing a freshly prepared solution of prednisolone-21-phosphate (prednisolone equivalent 20 mg. in 100 ml. normal saline solution) is described.

The value of the method has been shown by means of a "double-blind" trial employing sequential analysis, and by further use in 20 patients.

This method is particularly applicable to cases of ulcerative colitis involving the distal part of the colon, and should be used early in any acute or relapsing case.

I would like to thank Dr. John M. Naish for his encouragement and help; Dr. R. J. Sandry for help with the histology; Dr. K. H. Gaskell for radiological advice; Dr. P. Armitage for help with the sequential analysis; Glaxo Laboratories for generous supplies of prednisolone 21-phosphate tablets, the pharmacy staff of Southmead Hospital for their help; and Mr. W. Sweet for the photographs.

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STAPHYLOCOCCAL SEPTICÆMIA TREATED WITH VANCOMYCIN IN THE PRESENCE OF CHRONIC RENAL FAILURE

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THIS report describes the use of vancomycin in the treatment of a patient with staphylococcal septicæmia in the presence of poor renal function. The responsible organism, *Staphylococcus aureus*, was resistant to most of the available antibiotics.

Our reasons for reporting this case are, firstly, that infection with antibiotic-resistant staphylococci is becoming more common in hospitals; and, secondly, that the treatment of such patients with vancomycin, even if they have poor renal function, is effective and relatively simple.

Vancomycin is an antibiotic, first isolated from *Streptomyces orientalis* by McCormick et al. in 1956. It is bactericidal and thus differs from almost all other antibiotics except penicillin and streptomycin. No staphylococcus so far tested has shown resistance to vancomycin (Garrod and Waterworth 1956).

The drug is poorly absorbed from the alimentary tract, is too irritant for intramuscular use, and therefore is given intravenously—preferably in dilute solution over a period of several hours. Thrombophlebitis at the site of injection and deafness are the main complications of its use. Thrombophlebitis does not occur if dilute solutions of the drug are used. Deafness is due to damage to the eighth nerve and has been reported with high serum concentrations of the drug (e.g., 70–100 μg. per ml.) (Geraci et al. 1958)—usually the result of impaired renal function. Vancomycin is excreted almost entirely by the kidneys; hence care is needed if renal function is suspect. Such high serum levels can be avoided if the dosage is controlled by daily serum-vancomycin assay. A serum level of 12 μg. per ml. is therapeutically effective.

Case-report

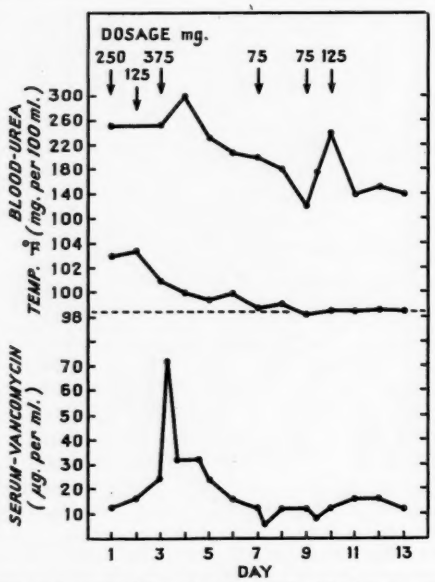
A 10-year-old schoolboy was admitted to the Royal Belfast Hospital for Sick Children in April, 1959, with acute pyelonephritis. Previous episodes of pyelonephritis, associated with posterior urethral obstruction and bilateral hydronephrosis, had seriously impaired his renal function. On this admission, his blood-urea was 250 mg. per 100 ml. and his urinary specific gravity was fixed.

An infection developed in the drip site at his right ankle. The infecting organism was identified as *Staph. aureus*, resistant to all available antibiotics except erythromycin, neomycin, and vancomycin: it was later reported to be slightly sensitive to chloramphenicol. By this time, septicæmia had developed, associated with septic arthritis of the right elbow-joint and the right hip-joint. An organism identical with that which caused the drip-site infection was isolated from the elbow-joint.

Treatment with erythromycin and chloramphenicol was started and continued for six days. In addition, the patient was nursed in a side-ward in the strictest isolation. During treatment with these two antibiotics the infection did not spread further, but staphylococci were still present in both the drip site and the elbow-joint and there was no clinical improvement. We felt that erythromycin and chloramphenicol, being bacteriostatic, would not eradicate the infection. We therefore decided to try vancomycin.

Because of the boy's poor renal function, control of the vancomycin dosage by serum assay was essential to avoid dangerously high serum levels.

For each assay, 8 dilutions of the patient's serum were made (1 : 2 to 1 : 32) with Wright's broth in 1 ml. volumes using 9 × 1 cm.



Dosage and serum levels of vancomycin, blood-urea levels, and body-temperature.

tubes. Tube sensitivities to vancomycin were prepared at the same time, diluting the vancomycin solution with human or horse serum to 1 ml. amounts containing 0·5–4·0 µg. vancomycin per ml. 0·02 ml. of 18-hour broth-culture of the patient's *Staph. aureus* was added to all the tubes. These were incubated at 37°C for 6 hours; to ensure adequate aeration, they were shaken by hand at hourly intervals. The end-point—i.e., the first tube showing no growth—could be read at 6 hours. Unlike Dutton and Elmes (1959), we were unable to obtain a reliable end-point any earlier. The serum-vancomycin levels were estimated by comparing the two groups of titrations and interpolating from the tube-sensitivity series into the serum-dilution series.

The drug was given through a polyethylene catheter into the inferior vena cava. A single daily dose, diluted in 5% glucose was given over a 4-hour period, and blood for serum assay was taken at least once a day. 5% glucose (500 ml. per 24 hours) was used to keep the catheter patent.

The dosage used, the serum levels, blood-urea, and body-temperature are shown in the accompanying figure. The initial dose of 250 mg. of vancomycin was based upon that used by Dutton and Elmes (1959) to treat their adult anuric patient.

The estimates of serum levels on the first and second days were thought at first to be unreliable, hence the increasing dosage on the second and third days (see figure); but there were signs of improvement on the second day, in that the temperature fell and the drip wound became sterile. That the original estimates of serum levels were accurate is shown by the response to the needlessly high dose given on the third day, which produced a serum level of 72 µg. per ml.; this fell in 6 hours to 32 µg. per ml. No further vancomycin was needed for 3 days, by which time the serum level had fallen to 12 µg. per ml., and thereafter 75 mg. on alternate days was enough to keep the serum level at the optimum 12–16 µg. per ml.

Cultures from the drip site were sterile on the second day, and this site remained free of staphylococci although *Pseudomonas pyocyanea* was isolated on the fourth day. A total dose of 0·955 g. of vancomycin was given in 10 days. There were no toxic effects, and no difference in auditory acuity was found on clinical testing after treatment. (Unfortunately, accurate audiometric testing was not possible.) The vancomycin eradicated the staphylococci within 48 hours of starting treatment; the patient's condition improved dramatically; and, with the exception of the third day, accurate control of the serum-vancomycin level was maintained throughout.

The blood-urea tended to fall throughout treatment, except for a rise on the tenth day. This was the result of a blood-transfusion rather than the vancomycin. (This is a well-recognised risk of blood-transfusion in patients with poor renal function.)

2 weeks after treatment finished, the site of the original infection had healed and all clinical signs of infection were gone from both hip and elbow joints. Renal function, although still poor, was no worse; the patient's weight had increased from 20 to 28 kg.; and he was well enough to enjoy television from a wheel-chair.

Discussion

Patients with poor renal function and uræmia are particularly susceptible to infection when in hospital, and an increasingly common hazard in this situation is infection with antibiotic-resistant staphylococci. The treatment of such infections is unsatisfactory. The less commonly used antibiotics may in theory be effective, but, because they are bacteriostatic and the patient's resistance is low, they are incapable of eradicating the staphylococcus.

In vancomycin we have a bactericidal drug which will rapidly kill staphylococci in most cases. Resistance to it has not been reported, and when it is properly used with serum assays toxic effects are unusual.

The method we used to control dosage is suitable for use in patients with poor renal function. It presents no difficulties to the clinician or to the clinical pathologist, and in our experience caused no disturbance either to the ward or to laboratory routine. We feel that a caval drip is a great help in the management of these patients because thrombophlebitis is no problem, the patient is more comfortable, and blood samples are more easily obtained.

In some cases the staphylococci may only be suppressed, not eliminated; and when treatment stops they reappear. Dutton and Elmes (1959) suggest that repeated and prolonged treatment is the answer in these uncommon cases. Even under these circumstances staphylococci do not become resistant.

A more common complication is replacement of staphylococci by *Ps. pyocyanea*, which is unaffected by vancomycin. This occurred in our patient; but, as the organism was present in his urine before treatment started, this was not unexpected. Fortunately, only the superficial site at his right ankle was involved and local neomycin was rapidly effective in eradicating *Ps. pyocyanea*.

Damage to the eighth nerve is common where high serum levels of vancomycin occur, as a result either of impaired renal function or of excessive dosage. This risk must always be remembered, and frequent audiometric tests are advisable in cases where renal function is suspect. Control of the dose by serum assay is essential in such cases.

Despite these risks we feel that vancomycin is a useful addition to the therapy available for the treatment of staphylococcal infections; and, with the technique described, it can safely be used even in the presence of poor renal function.

We would like to thank Mr. Ian Fraser, F.R.C.S., for permission to publish this report and Dr. P. C. Elmes for his advice. We would like to express our appreciation to the medical, nursing, and laboratory staff of the Royal Belfast Hospital for Sick Children for their help in caring for this child.

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NEONATAL PURPURA WITH PLATELET ISO-ANTIBODY IN MATERNAL SERUM

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THREE varieties of neonatal thrombocytopenic purpura are believed to exist. The first is caused by a congenital absence of megakaryocytes, and the second is found in infants born to mothers with idiopathic thrombocytopenic purpura. In the third variety, thrombocytopenia occurs in infants born to mothers whose platelet-count is normal. Such cases have been attributed to the sensitisation of the mother by previous pregnancy or blood-transfusion, with the subsequent development of antibodies to her infant's platelets. The unequivocal demonstration of platelet antibodies has, however, not hitherto been easy. We report here a case in which such antibodies were clearly demonstrated by the mixed antiglobulin reaction.

A multigravida, aged 24, was admitted in labour on Oct. 31, 1958, and gave birth the same night to a full-term male infant, weight 8 lb. 8 oz., after a normal labour. The baby appeared normal except for blueness of the face which persisted for several hours. The next day he was noticed to have a generalised petechial rash. Later some ecchymotic lesions up to 2 cm. in diameter were noted. On the second day he vomited dark-brown material but over the next three days the rash faded and subsequent progress was uneventful. The spleen was not palpable. The only treatment given was 2 mg. ' Synkavit ' on the first and second days.

Hæmatological investigations of the baby showed:

Date	*Hb g. per 100 ml.*	*Platelets per c.mm.*
Nov. 3, 1958	19.0	12,000
„ 5, „	...	7000
„ 15, „	14·4	80,000
Dec. 13, „	...	127,000
Jan. 5, 1959	9·9	230,000
Feb. 26, „	11·5	150,000

On Nov. 3 the bleeding-time was 9 minutes and the white-cell count 7800 per c.mm. (polymorphs 39%, eosinophils 5%, basophils 1%, lymphocytes 44%, monocytes 11%).

The mother's obstetric history was:

1954. Miscarriage at 16 weeks.

1955. Delivery of a normal female infant who showed no abnormality at any time. Six days postpartum the mother's hæmoglobin was found to be 7·2 g. per 100 ml. and she was transfused with two pints compatible group-O rhesus-positive bank blood.

1958. During the course of the third pregnancy her hæmoglobin was found to be 7·6 g. per 100 ml. on Oct. 10, 1958, and two pints of compatible group-O rhesus-positive four-day-old bank blood was given without any reaction. On Nov. 4, the fourth day after delivery, the hæmoglobin was 11·6 per 100 ml. and the platelets were 340,000 per c.mm. On Dec. 13 the hæmoglobin was 13·9 g. and the platelets were 230,000.

Serological Investigations

The red-cell groups of the father, of the baby, and of the mother after delivery were investigated by Dr. Weiner at the Birmingham Regional Transfusion Centre. The mother was confirmed as group-O rhesus-positive, the most probable genotype being CDe/CDe. The cells were Kell-negative and Fy (a+). The baby was found to be group-O rhesus-positive, the most probable genotype being CDe/cde. The direct antiglobulin test on the red cells was negative in both mother and child. The father was group-O rhesus-negative, cde/cde, Kell-negative, and Fy (a+).

The mother's postpartum serum was tested against a large red-cell panel including the baby's cells, and no evidence of a red-cell antibody was found. It was also examined for antibody against the father's red cells using saline and albumin suspensions, papain-modified cells, and the indirect antiglobulin reaction. Uniformly negative results were obtained, indicating the absence of antibodies against any red-cell antigen of the father.

In view of the occurrence of thrombocytopenic purpura in this child in the absence of any history or sign of thrombocytopenic purpura in the mother we decided to examine the maternal serum for platelet antibodies by the mixed antiglobulin reaction (Chalmers et al. 1959). In this test platelets are incubated with the serum to be examined, washed, and added (together with antiglobulin serum) to red cells which have been sensitised with a human incomplete antibody. If the serum contains an antibody against the platelets, mixed agglutinates of platelets and red cells are obtained. In this case positive mixed agglutination reactions were obtained when platelets from the father and ten normal people were treated with the mother's serum to a titre of 1 in 320. In contrast, similar treatment of the mother's own platelets with a 1/2 and 1/20 dilution of her serum gave completely negative results. A positive reaction was also obtained when the same technique was used to demonstrate the presence of leucocyte antibodies in one preparation.

Discussion

Six previous reports have been found of similar cases in which the maternal serum was stated to contain platelet antibodies (Harrington et al. 1953, Schulman et al. 1954, Stefanini and Dameshek 1955, Tullis 1956, Mahon et al. 1957, Moulinier 1958). The difficulty of obtaining stable platelet suspensions for agglutination tests is well known and the possibility of non-specific clumping has to be borne constantly in mind when a direct agglutination reaction is used as in four of these reports (Harrington et al. 1953, Schulman et al. 1954, Stefanini and Dameshek 1955, Tullis 1956). The mixed antiglobulin agglutination reaction, however, does not depend on obtaining a stable platelet suspension; for, although the platelets may adhere to one another non-specifically, they do not form mixed clumps with the red cells unless they have been sensitised by antibody.

In the case described by Moulinier and his colleagues the antibody, named anti-Duzo, was detected by the antiglobulin-consumption test, no agglutinin being demonstrable.

In the case reported here specific platelet and leucocyte antibodies appear to have been produced without any demonstrable red-cell antibody. It is not possible to say how far their production was caused by the two previous pregnancies and how much by the two blood-transfusions. It is of interest that the infant recovered as quickly with no specific therapy as the one described by Stefanini and Dameshek who was treated with corticotrophin.

Summary

The mixed antiglobulin reaction has been used to demonstrate the presence of platelet and leucocyte antibodies in the serum of the healthy mother of a child with neonatal thrombocytopenia. The platelet antibody was active against the father's platelets but not the mother's. The serum contained no demonstrable antibody against the father's red cells.

We should like to thank Mr. L. M. Park for first bringing the case to our notice and Dr. W. Weiner for examining the serum for red-cell antibodies.

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A CASE OF MAGNESIUM DEFICIENCY FOLLOWING MASSIVE INTESTINAL RESECTION

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BECAUSE of the lack of suitable routine methods of estimation (*Lancet* 1959) the relation between magnesium metabolism and human disease has received comparatively little attention, although patients who were considered to be suffering from magnesium lack have been described. The criteria for diagnosis of magnesium lack have usually been a low serum level and a good response to treatment, during which, in some instances, a positive magnesium balance has been demonstrated. The clinical syndrome is commonly a neurological one, with irritability, tremor, delirium, and convulsions, but some authors have described a calcium-resistant tetany.

Normally the renal conservation of magnesium is excellent (Fitzgerald and Fourman 1956), and a magnesium-losing renal lesion does not seem to have been recorded. Thus when magnesium lack has been encountered it was nearly always associated with inadequate food intake, often coupled with excessive intestinal losses. An association with parathyroid disease (Harman 1956, Potts and Roberts 1958) and osteochondritis (Miller 1944) has also been noted.

Magnesium deficiency has been described in patients receiving prolonged parenteral alimentation with magnesium-free fluids, and in patients with ulcerative colitis and ileostomy (Flink et al. 1954, Hammerstein and Smith 1957, Card and Marks 1958), or with chronic alcoholism, delirium tremens, and hepatic cirrhosis (Suter and Klingman 1955, Flink et al. 1957, Randall et al. 1959).

Our present case seems to be the first in which magnesium deficiency has been recorded as following massive resection of the small intestine—a condition which often presents clinical problems of some difficulty including diarrhœa, wasting, and tetany (Pullan 1959). The studies made during the patient's recovery emphasise the importance of an adequate supply of magnesium during the repletion of grossly wasted muscle masses. The condition observed may be compared with that of growing animals on low magnesium diets (Kruse et al. 1932, Smith 1959).

Case-report

The patient was a housewife, aged 39, admitted to the Little Bromwich General Hospital on Nov. 25, 1958 [no. 26483].

History

Except for an acute appendicectomy 8 years previously she had enjoyed good health, and she had borne two children with normal pregnancies and labours. 5 months after the last birth, and 7 months before admission to Little Bromwich, she had an acute abdominal catastrophe and after 3 days was admitted to the George Eliot Hospital, Nuneaton, under the care of Dr. E. A. Hoare. At laparotomy a large loop of small bowel was found to be twisted round an old adhesion. About 2 metres of infarcted gut was resected, with end-to-end anastomosis. After 4 weeks she was discharged reasonably well, though with some diarrhœa. A fortnight later she was readmitted because of weakness and was found to have hypokalæmia. After an intravenous infusion of potassium, she had a grand-mal seizure and her blood-pressure was elevated.

During the next 5 months she was readmitted to the George Eliot Hospital four times because of potassium deficiency and diarrhœa, the serum-potassium being as low as 1·3 mEq. per litre. With oral potassium chloride, the deficiency was corrected in hospital, but she relapsed after discharge, though she was supposed to continue the medicine.

2 weeks before admission to Little Bromwich, another laparotomy was performed and it was found that though the gut anastomoses were well healed, only 40 cm. of (hypertrophied) bowel remained between the duodenojejunal flexure and the ileocæcal valve. The potassium supplement was changed from chloride to citrate and within 48 hours she developed tetany, which responded to parenteral calcium gluconate. Immediately before admission she had been treated with high-protein diet with potassium chloride and vitamins A, C, and D by mouth. Vitamin-B complex had been injected.

Condition on Admission

She was apathetic and lay quietly in bed. Though she was oriented to her surroundings, her memory of her home circumstances was indistinct. Her only specific complaint was of diarrhœa.

Height: 161·5 cm. Weight: 36 kg. Expected weight: 62 kg. Weight before gut resection: about 58 kg. Total body-fat, measured with skinfold callipers (Fletcher 1959): 1·5 kg.

There was gross emaciation and she could not stand without support. The abdomen was distended and the most recent wound was incompletely healed. The ankle reflexes were absent but physical examination was not otherwise remarkable.

Investigations

Hæmoglobin, 10·6 g. per 100 ml.; mean corpuscular volume, 97 cμ; mean corpuscular hæmoglobin concentration, 30%. Serum-potassium 3·3 mEq. per litre, calcium 3·05 mEq. per litre, inorganic phosphorus 2·5 mg. per 100 ml., alkaline phosphatase 4 K.A. units per 100 ml., and albumin 2·8 g. per 100 ml. Urine nitrogen averaged 5·0 g. daily. Electrocardiogram was normal.

Intestinal function.—There was gross malabsorption. The stools ranged from 300 to 3000 ml. per day and contained on average 50 g. of fat and 6·0 g. of nitrogen. After an oral dose of 5 g. of xylose, 12·2% was excreted in the urine in 5 hours. After 50 g. of glucose by mouth, the blood-glucose showed a maximum increment of 32 mg. per 100 ml.

Magnesium.—The serum-magnesium was found to be 0·25 and 0·15 mEq. per litre, our normal range being 1·5 to 2·2 mEq. The urine-magnesium was also very low, being about 0·1 mEq. per day.

Progress

After a week in hospital on a normal diet, containing 15–20 mEq. magnesium daily, the patient had gained no weight and her condition was substantially unchanged. She was then given potassium chloride (50 mEq. K per day) by mouth, the same dose as she had been having previously, and calcium-lactate tablets (17·5 mEq. Ca per day). An injection containing vitamins A, B complex, B_{12}, C, D, K, and folic acid, was given weekly. Magnesium hydroxide was given as 20 ml. per day of the *B.P.* mixture, which contained 60 mEq. magnesium daily. After 6 days the calcium was discontinued.

Within a week there was a remarkable change in her condition. She became entirely clear mentally, began to take an interest in her appearance, and bought several fashion magazines. The improvement continued and within a few weeks she was symptom-free and anxious to return home. 48 hours after the magnesium supplement was begun, her weight began to rise steeply and steadily, and it continued to do so for the rest of her hospital stay. The diarrhœa steadily abated. She gained a total of 12 kg. in 75 days. As measured with skinfold callipers, 5·5 kg. of the weight gain was fat.

Before discharge, her intestinal function was reassessed and a considerable improvement was found. On average, the stools were 200 ml. a day, containing 10 g. of fat and 1·6 g. of nitrogen. Xylose excretion was 18% in 5 hours. Radiography showed delayed transit through a dilated small bowel: barium had not reached the cæcum in 2 hours. On the radiographs, the centre of the lumen of bowel measured 70 cm. from the pylorus to the ileocæcal valve. It is interesting to compare these findings with radiographs taken soon after the gut resection. The length of remaining bowel was exactly the same, but on that occasion the transit was rapid and barium reached the cæcum in 30 minutes.

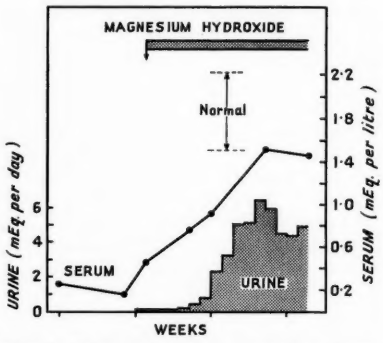

Fig. 1—Urine and serum magnesium levels at the beginning of treatment.

Follow-up

5 months after discharge from hospital, the patient was symptom-free and leading an active life. The bowels were open twice a day and the stools were usually formed. However, the magnesium and potassium levels in the serum and urine had fallen, and it was suspected that she had not been taking her magnesium and potassium supplements regularly.

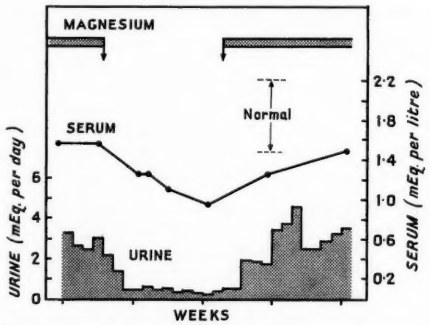

Fig. 2—Urine and serum magnesium levels when the magnesium supplement was withdrawn seven weeks later.

Studies on Magnesium and Calcium Metabolism

When the magnesium supplement was given, the serum-magnesium level gradually rose to normal. After 4 days, magnesium was excreted in the urine in increasing amounts (fig. 1). Towards the end of the patient's stay in hospital, she was so well that it was thought justifiable to stop the magnesium supplement, a full normal diet still being given. The urine magnesium decreased abruptly though it was never as low as previously. The serum-magnesium level fell more slowly, but became markedly subnormal. When the magnesium supplement was restored, the changes were reversed (fig. 2).

There were considerable changes in calcium metabolism. On admission, calcium levels were reduced in the serum and negligible in the urine. As soon as the magnesium supplement was given, the urine-calcium rose quickly to supranormal levels and then slowly declined. The serum-calcium rapidly became normal. When the magnesium supplement was discontinued, the serum-calcium remained unchanged. The daily excretion of calcium in the urine fell at once to about 30% of its previous level, rising slowly when the magnesium supplement was resumed. The calcium levels in urine and serum are shown in fig. 3.

A balance study was made over a period of 18 days, including the time when the magnesium supplement was stopped. At first, the magnesium balance was positive by 50 mEq. per day. Without the supplement, the balance was still positive but only by 8·0 mEq. per day. The nitrogen, potassium, calcium, and phosphorus balances were positive and did not change in the short period studied (see table).

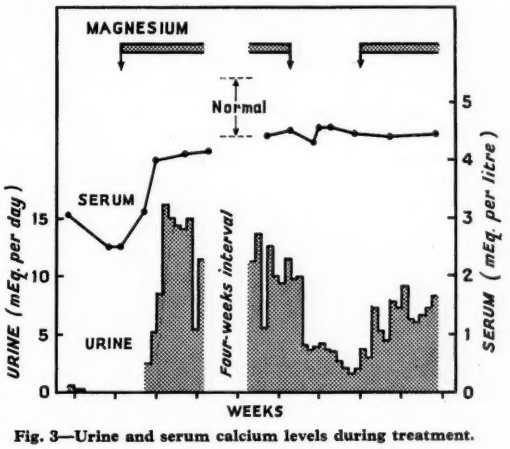

Fig. 3—Urine and serum calcium levels during treatment.

Discussion

It has been customary of late to write of "magnesium depletion" and it has been said (*British Medical Journal* 1958) that magnesium "deficiency" should not be claimed unless retention of magnesium (i.e., correction of deple-

BALANCE STUDIES IN SUCCESSIVE PERIODS WHEN MAGNESIUM WAS WITHDRAWN

Period	Magnesium (mEq. per day)				Nitrogen (g. per day)			Calcium (mEq. per day)			Phosphorus (g. per day)	Potassium (mEq. per day)
	Intake	Urine	Stool	Balance	Urine	Stool	Balance	Urine	Stool	Balance	Balance	Balance
1	91·1	3·1	14·5	+73·5	11·7	1·4	+8·3	13·3	21·4	+80·3	+1·47	+107
2	89·4	3·0	43·5	+42·9	10·1	3·6	+6·8	11·2	64·8	+43·5	+0·87	+ 49
3	89·2	2·7	38·0	+48·5	9·2	3·4	+4·3	10·4	54·9	+45·7	+0·80	+ 59
4	33·6	1·7	39·5	− 7·6	11·1	4·7	+6·8	9·8	85·1	+39·4	+0·80	+ 38
5	29·8	0·7	15·4	+13·7	9·4	2·9	+7·8	5·2	43·6	+59·2	+0·99	+ 64
6	29·1	0·5	9·2	+19·4	10·6	2·2	+6·5	4·0	31·2	+80·2	+0·99	+ 76
7	33·2	0·4	26·5	+ 6·3	10·5	5·2	+6·1	3·6	104·0	+21·4	+0·49	+ 25
8	34·7	0·4	31·5	+ 2·8	11·9	9·0	+1·9	2·3	115·6	+ 6·8	0	− 18
9	30·0	0·3	15·5	+14·2	10·6	3·6	+5·0	1·9	56·3	+59·7	+0·71	+ 59

Each period comprised two days. Note reduction in magnesium intake at period 4. Nitrogen intake averaged 20·6 g. per day, calcium intake 119 mEq. per day (2·39 g.), phosphorus intake 2·58 g. per day, and potassium intake 170 mEq. per day, being approximately constant throughout.

tion) was demonstrated on treatment. It is true that the normal person can lose some magnesium—presumably from the bone store—without any change in the serum level or untoward general effects (Fitzgerald and Fourman 1956). But a lowered serum-magnesium level probably means that some depletion has taken place (Randall et al. 1959); and the term " deficiency " can reasonably be used, we think, if the serum-magnesium is substantially reduced and improvement occurs when magnesium is given.

It is well known that after massive resection of the small gut there is a period of severe malabsorption, followed after a few months by hypertrophy and dilatation of the remaining small intestine and a substantial improvement in absorptive capacity (Jackson 1958). In our patient, though the remaining small gut had hypertrophied, there had been little recovery of absorptive power. Consequently she was cachectic and lacked calories (low body fat), protein (low urine nitrogen), potassium, calcium, iron, phosphorus, and magnesium at least. The magnesium depletion appears to have been exceptionally severe, as judged by the extremely low levels in urine and serum. Fitzgerald and Fourman (1956) postulated that because of the small amount of magnesium in the intestinal secretions (1 to 3 mEq. per litre), excessive losses from the gastrointestinal tract are unlikely. This argument appears to have been falsified by our experience, though it is not possible to say whether prolonged copious fluid losses at those or higher concentrations were responsible.

Because our patient seemed critically ill, we used several therapeutic measures simultaneously. Potassium chloride was given but only in the same dosage as the patient had been having for several months. Oral calcium lactate was given but only for six days. Apart from the route of administration, the only difference in the vitamin therapy was the addition of folic acid and cyanocobalamin (B_{12}). In the absence of macrocytic anæmia, buccal ulceration, and sore tongue, it seems unlikely that either of these were in such short supply as to impair gut function seriously. Apparently, therefore, the beneficial effects of the therapy were due almost entirely to the administration of magnesium hydroxide by mouth and the rapid correction of the magnesium deficiency. It is possible that this supplement, being in inorganic form, was more rapidly available for this patient than much of the magnesium in the diet.

The result was dramatic and the patient's recovery remarkable. Steady progress was made, with gain in weight and substantial improvement in the absorptive capacity of the small intestine. It seemed that, with correction of the magnesium deficiency, the normal compensatory processes were able to return. The increase in transit-time through the small bowel may be of particular significance.

The metabolic changes observed were complex, and their interdependence and relative importance are not easily determined. Improvement in intestinal absorption during magnesium therapy was shown by the rise in urine volume and in urine-sodium and -chloride on a relatively constant diet. This rise occurred within 48 to 72 hours. However, the stool volume increased and fæcal fat was unchanged: they did not fall until 7 to 10 days after the start of treatment.

After 6 weeks' treatment—by which time intestinal absorption had considerably improved—a positive magnesium balance was maintained even when the supplement was stopped. The decline in the serum-magnesium at that time suggests, however, that the amount of magnesium absorbed was not sufficient to meet all requirements, including replenishment of the bone store and restoration of lean body mass.

The changes in calcium metabolism were striking. The rapid rise in serum-calcium (fig. 3) when the magnesium supplement was given may have been due to movement of calcium ions out of muscle cells in a manner reminiscent of the reciprocal ion movements between sodium and potassium. (To test this hypothesis, tissue analyses would be required.) When the magnesium supplement was withdrawn, less calcium was excreted in the urine but no change was detected in the level of calcium in the serum—which implies increased tubular reabsorption. The fæcal calcium rose but calcium balance was unchanged; so the net absorption from the gut must have fallen.

The relation between the serum-magnesium level and the total daily urinary magnesium loss is shown in fig. 4. This chart also contains data from another patient—a man of 45, with terminal chronic nephritis, who had taken regular doses of magnesium hydroxide for several years. When this remedy was stopped the serum-magnesium fell to normal. The data from the two patients are consistent and suggest that magnesium virtually disappears from the urine when the serum level falls below about 1·0 mEq. per litre. This seems to be the tubular threshold for magnesium, above which the urinary loss is proportional to the serum level. Similar conclusions can be drawn from the data of Chesley and Tepper (1958).

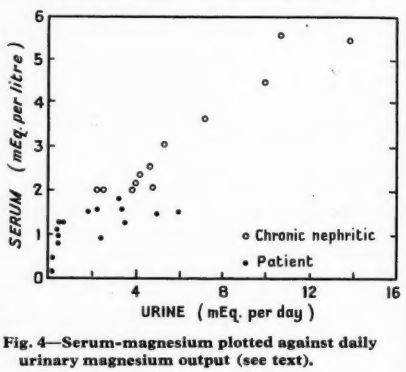

Fig. 4—Serum-magnesium plotted against daily urinary magnesium output (see text).

While much of our patient's recovery may be ascribed to the improvement in intestinal function, other factors may have operated. Probably, when an essential element such as magnesium is deficient, the normal processes of cellular repair are retarded even though the other essential substances are available. In our patient, the wasted lean tissue apparently could not be reconstructed until the supply of magnesium was adequate.

The symptoms and signs were not specific. Apathy, slight mental clouding and weakness were prominent but could have been caused by potassium deficiency. Tetany —with only moderate hypocalcæmia and no evidence of alkalosis—was also noteworthy.

The implications seem plain. Patients who have chronic diarrhœa with malabsorption and steatorrhæa may have magnesium deficiency; and examination for this deficiency may be desirable in patients who have undergone massive intestinal resection. Estimation of the magnesium in the serum and in twenty-four-hour urine is probably a good method of detecting it. Treatment with magnesium hydroxide by mouth is effective even in the presence of diarrhœa.

Summary

After massive resection of the small intestine a woman of 39 developed a malabsorption syndrome with wasting

and apathy. The magnesium levels in both serum and urine were found to be very low. Treatment with magnesium hydroxide by mouth led to immediate improvement followed by substantial recovery of intestinal absorptive capacity and restoration of body tissues.

Thanks are due to Sister M. McInnes and staff for the nursing care of the patient, to Mrs. L. Piercy for the dietary measurements, and to Mr. S. A. Gaunt for the photography. Dr. I. MacIntyre of the Postgraduate Medical School, London, kindly arranged for the flame spectrophotometric estimation of the fæcal magnesium.

Appendix

THE ESTIMATION OF MAGNESIUM

(A. A. HENLY and R. A. SAUNDERS)

Some of the best-known and simplest methods for estimating magnesium are those based on the Titan Yellow reaction. This reaction has adequate specificity for use with biological fluids and no special equipment or technical skill is required.

We have found polyvinyl alcohol to be the best of several reagents described for maintaining the magnesium hydroxide-dye complex in solution (Heagy 1948, Orange and Rhein 1951, Masson 1957). The reaction conditions have been studied carefully by Andreasen (1957). However, thiazole dye methods for magnesium have been criticised because of instability of the dye solutions, high and variable blanks, and the variation in sensitivity found with different batches of dye. Some of the difficulties are undoubtedly due to variations in the dyes used. These include Titan Yellow, Thiazole Yellow, Clayton Yellow, Chlorazole Yellow, and Mimosa (Mitchell 1954). Some of these are generic names for groups of dyes, which may vary in constitution according to the source and method of manufacture.

Several batches of dye were tested by paper chromatography and found to contain a variable amount and number of impurities which fluoresced under ultraviolet light. In one sample, which had a low sensitivity for magnesium, the main yellow component had a different RF value from that of the others. The absorption curves of the dyes and of their magnesium complexes, and also the blank values for a given dye concentration, showed substantial variations. Using a phenol-water preparative paper-chromatographic system, small amounts of partially purified dye were obtained. These gave lower blank values and better absorption curves than the starting materials but efforts to develop a method for purifying larger quantities have not yet been successful.

Our experiments indicate that the correct material to use for magnesium estimations is that defined in the Colour Index (1956) as Direct Yellow 9, C.1. 19540. The similar dye derived from sulphonated primuline is less satisfactory.

We use the following adaptation of the methods of Heagy (1948) and Orange and Rhein (1951) for estimating magnesium:

Reagents

(1) Oxalate buffer solution. Dissolve 6·75 g. ammonium oxalate and 0·315 g. crystalline oxalic acid in water to 500 ml.

(2) 0·1% polyvinyl alcohol (P.V.A.). Mix the powder into a smooth paste with a few millilitres of water and pour into a large volume of boiling water, as for starch solutions. After cooling, dilute to the required volume.

(3) 0·05% solution of Titan Yellow in 0·1% P.V.A. We have found the dye solution to be stable in the dark for several weeks. Filter before use. The best concentration of dye should be checked for each batch.

(4) 2 *N* sodium hydroxide.

(5) 1 *N* trichloracetic acid (16% w/v) (T.C.A.).

(6) Standard magnesium solutions. Prepare a stock solution containing 50 mEq. per litre using ' Analar ' magnesium acetate or sulphate. Dilute this as required to give solutions containing 1, 2, and 3 mEq. per litre.

Method

(a) *Serum, plasma, cerebrospinal fluid.*—Mix 1 ml. of sample with 2 ml. of oxalate buffer. Stand for 20 minutes and then centrifuge. The precipitate can be used for calcium estimation (Henly and Saunders 1958). Mix 2 ml. of supernatant liquid with 2 ml. of *N* T.C.A. and stand for 15 min. or longer. Centrifuge and transfer 2 ml. of protein-free solution to a test-tube. Add 1 ml. Titan Yellow solution and 2 ml. 2 *N* NaOH, mixing after each addition. Set up a blank and standards at the same time, using 1 ml. of water or of dilute magnesium standard solutions instead of the sample. Measure the orange-red colour against the blank at a wavelength of 540 mμ. The colour develops immediately and is stable for several hours.

(b) *Urine.*—The urine should be at pH 4 to 6. If the urine is protein-free, the method can be simplified by omitting the T.C.A. step. Mix 1 ml. of calcium supernatant with 1 ml. Titan Yellow solution and 3 ml. of *N* NaOH. Set up the blank and standards in the same way. If the magnesium level is low, mix 2 ml. of urine with 1 ml. of oxalate buffer and proceed as before. If the urine is highly pigmented it may be necessary to set up a urine blank—e.g., 1 ml. calcium supernatant, mixed with 1 ml. 0·1% P.V.A. and 3 ml. *N* NaOH. Measure the colour against water at 540 mμ and deduct the reading from the Titan Yellow colour reading.

(c) *Stools.*—The Titan Yellow method could not be used for stool magnesium in this patient because of interference by iron which she was taking by mouth at that time. The magnesium was therefore determined on ashed samples by flame spectrophotometry at 285 mμ according to the method of MacIntyre and Davidsson (1958).

It may be necessary to test several batches of dye before a suitable one can be found. The availability of a standardised dye of known purity would overcome this difficulty. With a satisfactory batch of dye, it is possible to obtain linear and reproducible calibration curves up to a magnesium concentration equivalent to at least 7 mEq. per litre of sample. The colour reaction is sensitive to concentrations of ions such as oxalate and trichloracetate, and also to pH, and these must be kept constant in blank, standard, and test solutions. Removal of calcium is not essential for the magnesium method and can be omitted if calcium estimations are not required.

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". . . Science has become a profession, just because it has begun to bear large-scale practical fruits. The trouble is that the professional man is expected to show results. His public standing depends upon his efficacy . . . As a matter of history, science became professionalised once before, and what followed was a disaster . . . Comfortably ensconced under government patronage in the museum at Alexandria—that great precursor of the Institute for Advanced Studies—scientists were tempted to concentrate . . . on doing things they were good at. Intellectual dissatisfaction had largely evaporated. Hero of Alexandria was busy designing obol-in-the-slot machines for dispensing holy water, and hydraulic singing-birds for use as ostentatious table-decoration. Ptolemy was finding better and better ways of preparing nautical almanacs. On its own ground, Alexandria was without doubt a great advance on anything the Athenians could show. Yet, comparing the modest craftsmanlike Alexandrian science with the more dashing and speculative theories of classical Athens, I myself cannot help regretting the results of professionalisation."—Prof. STEPHEN TOULMIN, *Listener*, Feb. 11, 1960; p. 252.

Medical Societies

LIVERPOOL MEDICAL INSTITUTION

A SYMPOSIUM on the Role of Inheritance in Common Diseases was held on Feb 18, under the chairmanship of Dr. E. N. Chamberlain, the president.

Dr. C. A. CLARKE said that it had long been realised that common diseases whose ætiology was obscure were due to a subtle combination of factors, some environmental and some inherited. In the past the "soil", although given due emphasis, did not really connote any specific characters, and it was passed off under such terms as the "constitution" or "diathesis" of the patient. Later there was some advance in that certain diseases were thought to be associated with bodily or mental characteristics. Thus, early greying of the hair was thought to predispose to addisonian anæmia, asthmatics were considered usually to be of dark colouring, and in duodenal ulcer various psychological types and certain physical traits were thought to predispose to the disease. The trouble with all these characters was that they could not be measured accurately. What was "early greying"? How dark was "dark"? How worried was a "worrier"? How John Bullish was a pyknic? In other words, these characters were not discrete but graded and were quite useless for assessing associations precisely.

In recent years, however, much more accurate genetic markers had been discovered—the blood-groups, the ability or inability to taste phenylthiocarbamide (P.T.C.), the secretion or non-secretion of the blood-group substances in the body-fluids, and the presence or absence of some protein groups such as the haptoglobins. In all of these intermediates were rare. Undoubtedly, some of these markers were associated with certain diseases, but the associations were often small and might be of little diagnostic or therapeutic importance. Nevertheless, in maintaining a polymorphism such as the ABO blood-groups it was such small effects that must be sought.

Peptic Ulcer

Dr. R. B. MCCONNELL said that the foundation for the recent advances was laid in 1951 when it was shown conclusively that heredity played a part in both duodenal and gastric ulcer, and that the high familial incidence of the disease could not be due entirely to the members of a family having a common environment. The familial pattern of inheritance would fit in with a polygenic inheritance, and recent research had been directed to finding out which genes were concerned. We now knew the identity of two of the genetic loci concerned in duodenal ulcer.

Group-O people were about 35% more liable than those of the other groups, and non-secretors are about 40% more liable than secretors. Taking the least susceptible people—the secretors of A, B, and AB—as a base-line, we found an increasing order of liability, with the group-O non-secretors, the most susceptible type, about $2^1/_2$ times more liable.

If it were not for the O gene and the non-secretor gene, there would be 20% fewer ulcer patients than at present. How these genes cause this differential liability was unknown. The most likely explanation was that they influenced the tissue resistance of the duodenum, and that an immunological mechanism was concerned. Alternatively these genes might be concerned in the type of gastric mucosa which was inherited, that of a group-O person responding to stimuli by producing larger quantities of acid than that of a group-A person. Rather in favour of this latter mechanism was the recent finding that the prevalence of group O in stomal ulcer was even higher than that in duodenal ulcer, and there was probably a more direct relationship between acid and stomal ulcer than between acid and duodenal ulcer. What was needed was study of the acid production of normal people to see if this was related to their blood-groups.

Erythroblastosis

Dr. RONALD FINN said that only 1 in about 20 rhesus-negative women married to a rhesus-positive husband becomes sensitised to the rhesus factor. Probably, therefore, protective mechanisms existed for 19 out of 20 such matings.

P. Levine was the first to suggest that ABO incompatibility was protective against erythroblastosis fœtalis. In a Liverpool series of 164 families with erythroblastosis the proportion of incompatible matings was 24%, and the immunising fœtus (when it could be determined with certainty) was always found to be compatible.

Using a modification of the Zipursky method for the detection of fœtal red cells, Dr. Finn had investigated the blood of 50 mothers within seventy-two hours of delivery. Fœtal cells were found in about a third of the compatible matings, but were never found in incompatible matings. This finding further supported the hypothesis that ABO incompatibility is protective.

Dr. Finn tentatively suggested that it might be possible to destroy any fœtal red cells found in the maternal circulation following delivery by means of a suitable antibody. If successful, this would prevent the development of erythroblastosis, so mimicking the natural protection afforded by ABO incompatibility.

Goitre

Dr. F. D. KITCHIN said that a familial disposition in thyroid disease was well recognised and conventional genetic studies had shown a more or less conclusive mode of inheritance in toxic diffuse goitre, and in the rarer conditions of familial goitrous cretinism, congenital deafness with goitre, and athyreotic cretinism. In simple goitre the results of pedigree studies had been conflicting since genetic effects were often overwhelmed by environmental factors.

Together with Dr. Howel Evans, by using the gene marker of the P.T.C. taster response (an example of human polymorphism) he had studied 447 patients with thyroid disease who had had thyroidectomy and in whom the gland was studied histologically. Statistical analysis indicated that the taster/non-taster genotypes were important in determining the type of thyroid disease that might develop. A highly significant deficiency in non-tasters (16·6%) was found in the group of toxic diffuse goitre and a significant excess of non-tasters in the multiple-adenoma group—greater in men (64·4%) than in women (36·2%). Dr. Kitchin presented a hypothesis of differential susceptibility to naturally occurring goitrogens of the thiocarbonamides class, based on the supposition that they might be transmitted to man through cow's milk.

Rheumatic Disease

Dr. J. C. WOODROW said that environmental factors undoubtedly played a predominant part in determining the incidence of rheumatic fever. Group-A hæmolytic streptococcal infection was essential, and poor environmental conditions were strongly conducive, to the production of the disease. Host factors must, however, play a part in the individual case because of the low incidence under optimal environmental conditions. Familial aggregation, in part genetic, had been repeatedly demonstrated. On the supposition that the pathogenicity of the hæmolytic streptococcus in the pharynx might be influenced in some degree by the presence or absence of particular locally secreted blood-group substances, these had been investigated in relation to rheumatic fever. Some combined figures from Liverpool and Taplow showed a significant rise in the percentage of non-secretors of A, B, and H substances which was being further investigated. Moreover patients who had had rheumatic fever included a significantly low percentage of group O. Attempts were being made to grow the hæmolytic streptococcus on media with and without A, B, H, and Lewis blood-group substances to find out whether there was any difference under varying conditions.

In rheumatoid arthritis no constant environmental factor was known, but there was a similar familial aggregation suggesting

a genetic factor. The rheumatoid serum factor was present in most, if not all, cases of rheumatoid arthritis and was believed to be intimately connected with the pathogenesis of the disease. Family studies had shown a significantly higher prevalence of positive tests for this factor in the relatives of patients with arthritis than in controls. Thus an abnormal γ-globulin which might be genetically determined could be a factor, and this was known to occur in other conditions.

A family study in Sweden suggested that a hypergammaglobulinæmic state was inherited, and that in a small proportion of cases systemic lupus erythematosus and rheumatoid arthritis supervened—presumably owing to other, unknown, factors. The majority of the members of the pedigree were symptomless and showed only a raised γ-globulin.

Tuberculosis

Dr. D. A. PRICE EVANS said that variations in susceptibility to communicable disease and variations in response to treatment had, in the past, been ascribed to the possession by different individuals of differing "diatheses" or inborn constitutional properties. Recent work on tuberculosis which he had carried out at the Johns Hopkins Hospital had brought more definite evidence to light. Plasma-isoniazid concentrations had been determined chemically six hours following ingestion (10 mg. per kg. body-weight) in 484 subjects. The frequency-distribution curve of these concentrations was bimodal. Individuals were divided by the antimode into rapid and slow inactivators of the drug. There was no heterogeneity for these characters due to sex or age, and on the numbers studied the distribution of phenotypes appeared to be the same in American Negroes as in whites. The numbers studied were too small to determine whether tuberculosis affected one phenotype more than another. 267 of the subjects studied constituted 53 white families. The family data were consistent with the hypothesis that the slow inactivator character was recessive. A "dosage" effect of the allele controlling the dominant character was demonstrable in that there was a significant difference between the mean plasma-isoniazid concentration of recognisable heterozygotes and the mean value of all other rapid-inactivator family members.

The principal speculations which followed these findings fell into four groups :

1. *Treatment.*—The slow inactivators of isoniazid might recover better from their tuberculosis when treated with isoniazid as they had higher blood concentrations. There was no satisfactory evidence on this point. The slow inactivators might also be more prone to the development of polyneuritis. Again there was no satisfactory evidence. It might be expected that rapid inactivators would be more prone to develop isoniazid-resistant tubercle bacilli. Conclusive evidence showed that this was not so.

2. *Susceptibility to tuberculosis.*—Was either phenotype more prone to develop the disease ? The answer was unknown as insufficient numbers had as yet been studied. It might be speculated that, if isoniazid-like compounds with tuberculostatic properties exist in Nature, the rapid inactivators might be more prone to develop tuberculosis.

3. *Were chemically related drugs subject to the same metabolic polymorphism ?*—The pharmaceutical market was being flooded with monoamine-oxidase inhibitors which were all substituted hydrazines. Variations in their metabolism, if present, might account in some measure for the variable results obtained by their use.

4. *The possibility of polymorphism* in the metabolism of a drug made the planning, and the assessment of results, of therapeutic trials (particularly those employing "fixed sample size") a matter of complexity. Such a possibility should be looked for before large trials were instituted.

Natural Selection in Man

Dr. P. M. SHEPPARD said that the data described in the symposium showed that certain inherited traits, such as the ABO blood-groups, secretor status, and P.T.C. taste response, were associated with some common diseases in such a way as to suggest that the genes responsible for the traits also affected susceptibility to the disease in question. It had long been known that two or more forms of a gene could not remain common in a population except under very specific conditions of opposing selective forces. Since there were two or more forms of a gene responsible for each of the nine major blood-group systems as well as for the secretor and P.T.C. taste-response characters, special opposing selective forces must be acting. Ford predicted in 1945 that associations with disease would be found involving the ABO, secretor, and P.T.C. taste characters.

These predictions had been confirmed. The diseases concerned are chiefly ones of middle or old age and therefore did not much reduce fecundity. Consequently it was safe to predict that other and more powerful effects of the genes concerned were yet to be found. One—the elimination of sperm, fertilised eggs, or fœtuses incompatible with the mother on the ABO system—was all but fully established. This would tend to eliminate groups A and B, not maintain them. There must therefore be yet other equally powerful effects operating, part of which might be concerned with the interaction of ABO and Rh in erythroblastosis. Of the nine blood-group systems only the MN system was known to have selective forces which would maintain more than one form of a gene in a population. Here MN x MN marriages produced an excess of MN children over what was expected from Mendel's first law.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

AT a meeting on Feb. 18 in London, Dr. T. F. DAVEY described his experiences in the treatment of leprosy at the great centre at Uzuakoli, Nigeria.

The great advance in recent years had been the introduction of the sulphones, and the reputation of dapsone (D.D.S.) had increased with time: it is cheap, effective, and so far has not led to the development of resistance; it may even have prophylactic value. But cure took a long time, and alternative drugs were keenly sought. One of the main problems had been to obtain evidence of the action of drugs on the leprosy bacilli themselves, and in the absence of successful cultivation techniques this became a matter of examining the bacilli as they existed in human tissues. There was evidence to suggest that as treatment proceeded and clinical improvement ensued, the bacilli in the tissues became more and more granular in appearance in stained section; the proportion found to be granular may therefore be taken as an indication of the effect of treatment, in conjunction with an estimate of the numbers of bacilli found in biopsy material taken from time to time. There was difficulty here, however, in that the bacilli were not uniformly distributed in the skin. Trials of new drugs were also subject to the difficulty that leprosy is sometimes hard to classify, and the prognosis is also variable, so it is difficult to ensure that patients treated with the trial drug are comparable with controls.

Here Dr. Davey made the important point that there can be no question of untreated controls—the standard of comparison is the patient treated with dapsone. Two drugs had recently been introduced. Ciba 1906 was useful in the early stages but might lose its efficacy after a year or more of treatment; it could be used with dapsone. 'Etisul' (of which the main constituent was ethyl mercaptan, and which had a strong smell) was also valuable (it had been given by inunction). Its action was rapid on bacilli of normal morphology, but it could probably best be used in conjunction with dapsone. Progress must be estimated by three strands of evidence—bacteriological, histological, and clinical—and the physician must know his patients.

Dr. R. J. W. REES showed slides to illustrate that when bacilli died their protoplasm shrank—as in *Mycobacterium lepræ-murium* after treatment with isoniazid—and this supported Dr. Davey's view that granular organisms were prob-

ably dead. The advantage of combined therapy was that it tended to prevent drug resistance.

Dr. G. W. DRIVER, who had synthesised etisul, observed that it had originally been screened in experiments on tuberculous animals. It acted only on mycobacteria, but not in vitro; it probably interfered with some unknown metabolic path in the monocytes. It could act systemically after inunction.

Dr. W. H. JOPLING said that patients with granular leprosy bacilli had proved unsuitable subjects for etisul. He emphasised the element of pain in leprosy (nerve pain or bone pain) and the difficulty of treating it; analgesics were only partly successful, and cortiscosteroids, though useful, had side-effects. Intraneural injections sometimes helped.

Dr. D. S. RIDLEY remarked that the bacterial index, though it had its limitations, remained a useful means of estimating progress.

Dr. K. R. CHATTERJEE suggested that granular leprosy bacilli may be regenerating forms, not degenerating. He had found Ciba 1906 useful in patients refractory to dapsone, and etisul valuable in combination with dapsone.

New Inventions

INSERTION OF INTRAVENOUS CATHETER

THE device illustrated here enables the insertion of a nylon intravenous catheter for routine " drips " as easily as the usual needle, and without local anæsthesia. The only special equipment necessary is:

(1) A nylon catheter of 0·5 mm. bore, cemented at one end into a female Luer (or Record) mount. A short length of nylon suture material is conveniently used as a stylet: this guarantees patency of the catheter lumen and prevents kinking and buckling of the thin-walled catheter tubing during manipulation. In routine ward practice, a 5·0 cm. length of this tubing has been found most convenient, being both long enough to permit easy handling and short enough to allow an adequate flow-rate—e.g., gravity-fed ' Dextraven ' at 74 drip-chamber drops per minute (100 drops equivalent to 7·0 ml.).

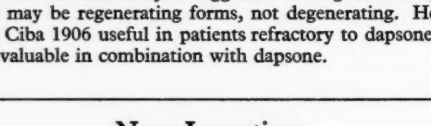

Fig. 1—Introducing needle, showing slot in shaft; and catheter, with contained nylon stylet.

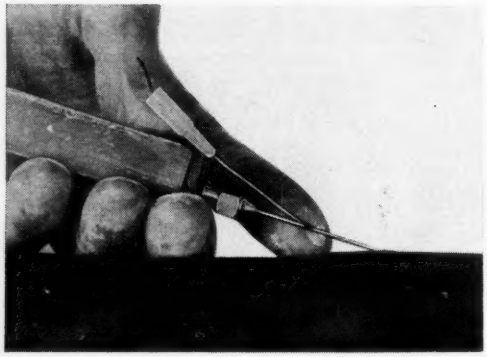

Fig. 2—Needle, with contained catheter, about to be introduced into vein.

(2) A metal introducing needle.

The catheter is first inserted into the lumen of the needle through the proximal widened part of the slot in the needle shaft, and passed to within a millimetre or so of the needle point. It is not inserted through the hub.

Using any convenient side-nozzle syringe as a handle, the needle, with contained catheter, is inserted into the selected

Fig. 3—Catheter fully inserted into vein, infusion running: needle still in situ.

vein in the usual way. The catheter is then easily pushed further into the vein, which is now decompressed, and the infusion started by simply connecting the drip set to the Luer fitting of the catheter after removing its stylet. The introducing needle, still in situ, is then removed, steadying the catheter to prevent its inadvertent withdrawal from the vein. The catheter parts company from the slot in the needle without difficulty. (The vein should always be deflated and the drip connected before removing the introducing needle; otherwise a small subcutaneous hæmatoma may result.)

This device has now been used in many cases for infusions of all the usual fluids, including blood, plasma, dextran,

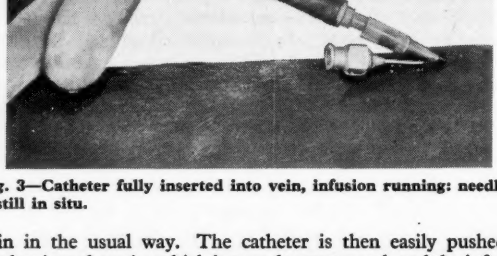

Fig. 4—Needle withdrawn: drip tubing about to be taped to the skin.

electrolytes, anæsthetic agents, and drugs: and, while the above size of catheter has proved eminently satisfactory, it should be noted that larger-bore catheters may be inserted in the same way if required for special purposes. Local anæsthesia is then, of course, required, as the introducing needle is correspondingly larger.

The catheter described here may be obtained from Portland Plastics, Ltd., Bassett House, Hythe, Kent, and the introducing needle from Messrs. Chas. F. Thackray, Ltd., 10, Park Street, Leeds.

My thanks are due to the Chief Secretary, Western Pacific High Commission, Honiara, for permission to publish; and to the medical officers and assistant medical officers in the service of the Government of the British Solomon Islands Protectorate, who have reported favourably on the device.

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Reviews of Books

Modern Trends in Accident Surgery and Medicine

Editors: RUSCOE CLARKE, F.R.C.S.; F. S. BADGER, F.R.C.S.; SIMON SEVITT, M.D., M.SC., F.R.C.P.I., Birmingham Accident Hospital. London: Butterworth. 1959. Pp. 346. 75*s*.

CHANGING conditions on the roads and in mechanised industries have greatly affected the number and type of injuries brought to casualty departments of hospitals in this country. Gross abdominal, intracranial, and thoracic injuries are increasingly common and now happen more often than before in combination with each other and with severe limb fractures. The complexities of diagnosis and treatment which ensue are among the reasons which have prompted such bodies as the British Orthopædic Association to urge that serious casualties should in future be concentrated in a comparatively few "designated hospitals". These same problems are considered at length in the latest addition to the Modern Trends series, for the book is concerned throughout with the management of major, rather than minor, forms of trauma.

Written by ten members of the staff of the Birmingham Accident Hospital, the chapters all indicate how radically our ideas on this subject are changing. The late Mr. Ruscoe Clarke, writing on wound surgery, points out that the war-time technique of excision has all but been abandoned. No longer is it the rule to excise all non-viable or doubtfully viable tissues, but rather to treat as autografts many tissues that would once have been sacrificed. Anti-gas-gangrene serum, we read, is of little use in either preventing or treating that condition. Nearly all clinical infection in plated compound fractures is due "to the compounding and not to the plating": and, when infection supervenes in these fractures, Mr. J. H. Hicks advises it is usually wrong to remove the metal forthwith. Recent research on traumatic uræmia, much of it conducted at Birmingham, shows that the condition can no longer be considered to originate in the tubules. Failure of glomerular filtration accords better with the facts; and, indeed, tubular function can often be shown to be active or overactive.

This stimulating book highlights the more recent advances in casualty treatment (such as the routine use of anticoagulants in elderly patients with hip fractures), and, moreover, throws into sharp relief many serious gaps in knowledge (there is, for instance, as yet no established treatment for fat-embolism.) It will be widely read by all who are interested in closing these gaps.

Free Associations

Memories of a Psycho-analyst. ERNEST JONES. London: Hogarth Press. 1959. Pp. 264. 25*s*.

MANY readers of Dr. Jones' famous volumes on Freud must be curious about the earlier background of the faithful biographer who made great contributions to psychoanalysis both in this and other countries. This well-written book will answer their questions.

A psychoanalyst would be expected to be more than ordinarily frank about himself, and on the whole Dr. Jones was very frank. Thus, after penning the first paragraph—a factual one about his birthplace in Wales—he comments that the earliest remarks of an analysis are often the most significant, and, with elegant use of the analytical method, he demonstrates an intriguing dynamic background to these few innocuous phrases. He traces his childhood days and early life in London where, as a brilliant if headstrong young man, he seemed bound for success in neurology before several misfortunes robbed him of this career.

Jones' life was dominated by two colossi: by Freud, of course, during the greater part, but before this by his fellow-countryman, Trotter, whose aphorisms shine forth every few pages. Trotter was every bit the rebel Jones was in his earlier days and encouraged him towards the mental aspect of neurology, saying, in 1904, that in hysterical convulsions "one sees only the blood trickling under the door, but we know nothing of what tragedy is being enacted within". Trotter was also the one to call attention to the writings of Freud, although as Jones became more closely associated with the analytical movement their relationship lost its intimacy: the book recalls that at an early psychoanalytical congress Trotter, disgruntled, commented symbolically that at least he was the only one there who could cut off a leg.

From Jones' impressions of the great figures present at the birth of psychoanalysis, it can be seen how their personalities may have guided developments. Adler, for example, was seen at that time as socially uncouth, "sulky and pathetically eager for recognition", while Jung was said to have a rather confused and mystical mind and to talk in "cloudy generalities". Freud's intellectual stature struck Jones at once. At the 1908 congress Freud lectured on one case for three hours without notes and then by universal acclaim continued for a further hour. That does not happen these days. Of other men, Kraepelin was "gruff", and Morton Prince a popular extrovert. Harvey Cushing asked Jones to analyse the distressing neurotic symptom that troubled him before each of his great brain operations, though Freud said later that it was as well for his genius that this was not done.

The book, started in 1944, was put aside until the work on Freud was completed, and Jones died, aged 79, shortly after taking it up again. The events from 1918 to 1958 are well summarised by his son.

Heredity and Evolution in Human Populations

L. C. DUNN, professor of zoology and director of the Institute for the Study of Human Variation, Columbia University. Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1959. Pp. 157. 20*s*.

THIS is an excellent and businesslike short account of elementary genetics, their application to man, and the broad outlines of some of the main problems now interesting human geneticists. It is both scientifically adequate and intelligible to non-biologists, and seems particularly suited to the needs of the doctor who is hazy about the precise evolutions carried out by the chromosomes, and who feels uneasy in the presence of exciting new work like that on human aneuploidy. Even those who have regular dealings with genetics will find it a useful and nonsense-free source of recent examples. Professor Dunn covers a remarkable range in a short space: the reader should end with a clear idea of the simplified outlines of classical genetics, of the meaning of mutation, polymorphism, genetic drift, and selection, of the general features of ethnic groups and genetic anthropology, and—perhaps the most valuable part—with a critical approach to the dangers of genetic generalisations about man. Non-medical readers will find it equally profitable; and it is a useful companion to the recent Reith lectures.

A History of Embryology

2nd. ed. JOSEPH NEEDHAM, F.R.S., fellow of Gonville and Caius College and Sir William Dunn reader in biochemistry in the University of Cambridge. Revised with ARTHUR HUGHES, PH.D., lecturer in anatomy in the University of Cambridge. London: Cambridge University Press. 1959. Pp. 304. 52*s*. 6*d*.

WITH interest in the history of medicine gathering momentum within the profession, a new edition of Dr. Needham's well-known work is particularly welcome. The first edition, which appeared in 1934, was very well received and has in fact been out of print for a number of years.

The form of the book remains unchanged and incorporates the relevant findings of recent studies. The scientific evolution of embryology is traced from the early speculations of the ancients to the factual observations and the nascent experimental approach of more recent times. The author has chosen the beginning of the nineteenth century as a convenient period at which to conclude his account, because the later development of embryology has seen such a large number of investigators and the tackling of such a variety of problems that it is impossible to deal with them on the same scale as has been

successfully applied to earlier periods. Although the story is principally of the development of embryological knowledge in Middle Eastern and Western civilisations, account is also taken of Chinese and Indian thought. Only consummate skill and understanding could have produced a book so instructive and at the same time a delight to read.

Napoleon Immortal

The Medical History and Private Life of Napoleon Bonaparte. JAMES KEMBLE, CH.M., F.R.C.S. London: John Murray. 1959. Pp. 307. 28*s*.

THE doctor who sets out to write a biography is sometimes at a disadvantage: his preoccupation with disease, and a knowledge of how it can affect a patient's character, may make him attach too much importance to the illnesses of his subject. The course of history has often been altered by a pathological process, but there have always been many other factors involved. It is a fact, for instance, that the destiny of the whole of Europe was changed by the laryngeal carcinoma that afflicted the Crown Prince Frederick in 1887. But only because the character of his successor, Kaiser Wilhelm, was so different from his own: and the Kaiser's character in turn can only partly be blamed on the brachial palsy with which a panicky midwife endowed him.

No such imbalance mars Mr. Kemble's excellent study of Napoleon, which deserves high praise as a fascinating work of punctilious scholarship. There are no wild flights of psychological theory, and no hobby-horses are ridden. Indeed the principal impression is of a man who, under conditions of great stress, enjoyed surprisingly good health until his premature death from a carcinoma of the stomach. The author discounts the widely held view that Napoleon suffered from epilepsy (although this at first seems the most likely explanation for the peculiar seizure which so embarrassed Mademoiselle George at a moment when, to quote Mr. Kemble, the Emperor was " in flagrante delicto "): but he does incline to a belief that he was the victim of hypopituitarism.

On two critical occasions, however, Napoleon's usually robust health did fail him. During June 17, 1815, the eve of Waterloo, he was almost prostrate with exhaustion, having spent the previous night in agony while his faithful Larrey treated him for prolapsed hæmorrhoids. It is probable that, by this date, Napoleon's destiny was already decided and that this illness only made his defeat more certain. But more significance attaches to the episode three years earlier when, at the very climax of his Russian campaign, he was seized with acute retention. For three days, during which he should have been pursuing a retreating enemy and consolidating a precarious position, he seems to have been confined to his quarters, racked with pain. To the elucidation of the diagnosis at this time, Mr. Kemble, who is a urologist, brings a specialist's knowledge, and here too he refutes the suggestion which has often been made.

Histonomy of the Cerebral Cortex

S. T. BOK, head of the Netherlands Central Institute for Brain Research and professor of neurobiology at the University of Amsterdam. Amsterdam: Elsevier Publishing Co. London: D. Van Nostrand. 1959. Pp. 434. 72*s*.

IT would be idle to pretend that this book is easy to understand. Beginning with the assumption that the measurement of morphological details by means of the microscope is a satisfactory basis for the explanation of function of the cerebral cortex, the author—whose work appears to be the result of massive joint efforts by himself and members of his department—outlines in painstaking detail the morphological implications of the curvature of the cerebral cortex, relations between perikaryon and nucleus, morphology of the dendrite tree, and the other structural factors regarding neuron size, association of neurons, and the structure of the cerebral cortex. This part of the work is set out in great scientific detail and there is a considerable portion of mathematical reasoning in the various chapters. Many readers may have difficulty in comprehending the validity of these mathematical statements, and turn with greater interest to the hypothetical implications contained mainly in the last chapter, entitled Histonomy and Hypothesis. Having established the existence of what he calls interfibral vacuoles, Dr. Bok asks whether these vacuoles constitute a specific organ of memory.

The book really represents a monument to the value of micro-measurement when applied to the cerebral cortex. It may not be a very lively contribution to our understanding of cerebral function, but the information contained in it stems from careful and painstaking delineation of the components of the cerebral cortex. With our extending understanding of the structure and function of the brain these measurements may prove of value to research-workers in the future.

Love in Action

FERNANDO HENRIQUES, M.A., D.PHIL. Oxon. London: McGibbon Kee. 1959. Pp. 432. 45*s*.

BOOKS about human sexuality are probably the most popular compilations from compilations. This one compiles from a wider field than usual—its author is an anthropologist who takes in the literature of his own field, and sources such as Kinsey, and Ford and Beach, to supplement Havelock Ellis, the original quarry from which sex books are still being cut. His book does, therefore, make available to a wider readership information which will be new to many. The illustrations include some which it is very useful to have in print: others are makeweights and barely relevant. The only serious reservation to a favourable general impression is to doubt whether the compilation outside the author's own field is implicitly reliable: Sanskrit names are consistently misspelt, Tibetan Tantrism confused with Indian—minor points, perhaps, but damaging to a book which many will use as a convenient reference. Dr. Henriques has been over-modest in keeping illustrations from the West Indian culture, which he knows intimately, to a minimum—many readers would have preferred them to a wider but sketchier range.

The Care of Minor Hand Injuries

ADRIAN E. FLATT, M.D., F.R.C.S., assistant professor of orthopædic surgery, State University of Iowa. St. Louis: C. V. Mosby Co. London: Henry Kimpton. 1959. Pp. 266. 71*s*. 6*d*.

THOUGH written with an eye to the established practitioner, this book would make a useful work of reference for the student during the important period of casualty training. Professor Flatt's experience of hazards industrial and otherwise extends from Iowa to east of Aldgate pump. The outcome is comprehensive (despite the title) but concise, for he does not permit himself to be discursive, yet makes amends with a list of recommended reading that gives access to alternative methods. Animal and human bites find a place—and our peripatetic correspondent will be interested to learn that even chipmunks can be responsible for rabies. Throughout there is evidence of the author's concern that the patient shall make a full return to his rightful employment—and this surely is the foundation of all good treatment of hand injuries.

A Short Textbook of Surgery (7th ed. London: J. & A. Churchill. 1959. Pp. 547. 45*s*.).—It was probably no coincidence that the seventh edition of this useful work fell due in 1959, for it then came of age. At such a moment we may look back—not in anger, but in gratitude to the author, Prof. C. F. W. Illingworth, who has successfully kept it young both in content and in size, for this edition has actually lost weight by almost 80 pages. The secret? A strict reducing diet: in this case all pabulum has been discarded as it became obsolete with changing surgical practice. As a result this book fulfils a very special function: it provides the background reading for the student as he starts clinical practice, rapidly giving him basic facts to which he can make fast in what at first appears to be a daunting *mare incognitum*. There are no frills: it is the springboard from which he will rise to wider reading and further understanding.

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B.M.A. or A.M.B.?

Professor ECKSTEIN's book *Pressure Group Politics: the Case of the British Medical Association*[1] raises directly or indirectly some questions of great importance to the profession in this country.

He begins by outlining certain hypotheses about the operation of pressure groups in general, in any political system. He points out that what he calls "pressure group politics" is a function of three main variables—the pattern of policy, the structure of decision-making both in Government and voluntary associations, and the political culture of the society concerned. In Britain these factors include the role of the Cabinet and executive, and the position of the bureaucracy. He shows that in the political culture of Britain unusual stress is laid on corporations, in the broadest sense of that term. "Governments", he says, "tend to be regarded not as sovereigns . . . but, in the pluralistic sense, as corporations among many other kinds of corporations." Hence it has become the practice for the Government to enter into discussions, and even negotiations, with all sorts of voluntary bodies which may be interested in projected legislation or some executive decision.

ECKSTEIN then traces the part played in the National Health Service by the B.M.A. as one such powerful corporation, which has been greatly strengthened by "the collectivisation of medicine". Far from being the chief enemy of the Ministry of Health and continuously at war with it, as is sometimes supposed, the B.M.A. "in its present form as a vast, highly bureaucratised and wealthy organisation . . . is engaged in constant co-operation" with the Ministry, "a highly useful adjunct to the Ministry's machinery of administration which, had it not already existed, the Ministry would have had to invent". "It is obviously a matter of great convenience for the Ministry", ECKSTEIN points out, "to have available a single organisation which can deal with it in the name of the whole medical profession; everything is simplified thereby, from the problems of the size of formal negotiating committees to the all-important matter of day-to-day contact and consultation between public and voluntary officials." The executive officers of the B.M.A., however, have a number of problems. These include their relations with the representative body (which may sometimes take policy decisions that the executive know to be unwise or impracticable), relations between the B.M.A. and the semiautonomous General Medical Services Committee and Central Consultants and Specialists Committee, and, most of all perhaps, relations with outside bodies, particularly the Royal Colleges. In considering "channels of influence", ECKSTEIN concludes that the B.M.A.'s influence on the Ministry of Health is by far the most important of its means of exerting pressure. Though disputes may get a good deal of publicity they are really no more than tiffs between allies—"the sort of quarrels inevitable among the best of friends and partners". Reviewing achievements and failures of the Association in the political field, he describes in some detail the negotiations in which the Government were persuaded to revise their views on the numbers of senior registrars, which he classes as a success, and the negotiations on remuneration, which, despite the Danckwerts award, he regards as a failure.

ECKSTEIN's book, written with remarkable insight and the detachment of an observer from another planet, is a considerable achievement; and he touches upon all the major problems which the B.M.A. is facing. But he is concerned only with the B.M.A.; and some of these problems need treatment of wider scope. The chief reason for this is the relationship of the B.M.A. with the consultants—a relationship complicated by both facts and feelings. Though not much more than 20,000 of its 74,000 members are in general practice, the B.M.A. is widely regarded as primarily representing that branch of the profession. Why should a minority, consisting of not more than a third of the membership, exert a disproportionate influence upon policy? One explanation is that the local organisation of the B.M.A. favours the influence of the general practitioner, and both in the representative body and on the council this greatly predominates. In order to balance it to some extent the B.M.A. set up the Central Consultants and Specialists Committee; but, whereas general practitioners on the whole have no other allegiance than to the B.M.A., consultants have attachments also to the Royal Colleges and Royal Corporations. The attention of these bodies to medical politics has been discontinuous. Until the National Health Service was established, those few consultants who were interested in medical politics naturally gravitated to the B.M.A., to which they made a valuable contribution. But when, after the war, plans for the Health Service had to be discussed with the Government, and it became clear that the interests of general practitioners and consultants might not be identical, many felt that the B.M.A. might not be able to speak for the two groups with equal vigour; and the Association was unable to resist the claim of the leaders of the Royal Colleges that they should take an active part in the discussions. After the passing of the National Health Service Act the hospital medical staffs, including the consultants, came to be represented, in their negotiations with the Ministry, by the Joint Consultants Committee, which comprised representatives of the English Royal Colleges, the Scottish Royal Corporations, and the Central Consultants and Specialists Committee, the last acting as a bridge between the colleges and

1. Pressure Group Politics: the Case of the British Medical Association. By HARRY ECKSTEIN (Stanford, California, U.S.A.). London: Allen & Unwin. 1960. Pp. 168. 16s.

corporations on the one side and the B.M.A. on the other.

The B.M.A., then, suffers from the fact that, though it claims to speak for the whole medical profession in this country, its machinery makes it unrepresentative; and its cumbersome attempts to overcome this—as by setting up the Central Consultants and Specialists Committee—have in some ways added to its difficulties. Some of the decisions reached by the council and the representative body have considerably shaken the confidence of consultants in its wisdom and responsibility. The colleges and corporations, on the other hand, suffer from their lack of interest in, and knowledge of, "medical politics", and often fail to recognise its importance nowadays to the ideals which are their primary concern. Their influence depends either on the leadership of a very few individuals, who are concerned about the relations between Medicine and the State, or on the tendency of consultants at moments of crisis to become belatedly aware of their responsibilities and take action—as when in 1957 they held the profession back from precipitate action to which the B.M.A. was urging it. But, all too clearly, such public division in policy is a bad basis for relations with the Government. The existing system made a mockery of the so-called Negotiating Committee, which dealt with the Government in 1955 and 1956, as it must with any negotiating body which cannot cope with its internal differences. Without unity the profession is severely handicapped in dealing with the Government on any major issue.

But how is unity to be attained? We need not look beyond NATO, or even the Commonwealth, to see how hard it is for a group of autonomous and democratic corporations to achieve common action. In Medicine it certainly will not be achieved without sacrifices all round. For the B.M.A. merely to add a few nominees of the colleges and corporations to a council on which they would be outvoted by the representatives of general practice, and which would have to carry out the policy of the annual representative meeting as at present constituted, would not make the Association acceptable as representative of the whole of British Medicine. Nor would the colleges and corporations be well advised to sell their independence of political action for so insubstantial a return. While the representative body of the B.M.A. might make some further concessions to achieve better representation of consultants, the general practitioners have so far shown no sign of being willing to surrender their dominant position in B.M.A. affairs. Even if they did, there would still be deep mistrust to be overcome; for, though consultants may have lacked political consciousness, the kind exemplified by the B.M.A. has often failed to appeal to them.

But if the B.M.A. cannot expect to speak for the whole profession, why is there not better cooperation between it and other medical bodies? Though mutual suspicions are one of the reasons, a more formidable one is that it has not even now accepted its own limitations. Its promotion and protection of consultant groups, and the fact that it is regarded by the public as *the* doctors' organisation, have made it, in ECKSTEIN's phrase, too "corporationist". Any body claiming universality finds it hard to recognise the validity of the orders of other denominations, and therefore to work with them. In a crisis, when cooperation between general practitioners and consultants is most desirable, the chief stress falls upon the Central Consultants and Specialists Committee—whose functions as a bridge are fulfilled with increasing difficulty as it is subjected to increasing tensions from either end.

To expect either the B.M.A. or the other medical bodies to abandon their autonomy would at present be unrealistic; but they should be prepared to cooperate truly, especially in times of crisis. The profession needs a body which not only gives the various branches of Medicine balanced representation but also can develop the kind of collective responsibility which enables it to rise above sectarian interests. Such a body might indeed speak for the whole profession to the Government. But to achieve this the B.M.A. would have to become a genuine part of an A.M.B.—an association of medical bodies.

Hepatitis after Inoculations

BETWEEN two and five months after inoculation with a syringe or needle that has previously been used for someone else without being subsequently sterilised, a person may develop hepatitis. The proportion so affected is probably small, but it is unmeasured for two main reasons: the first is that the long incubation period disconnects in the patient's mind the episode of inoculation from his ensuing illness, and the second is reluctance to probe too deeply into the connection between inoculations and hepatitis lest litigation be encouraged and generally beneficial prophylactic immunisations discredited. Thus we remain in the dark about the true incidence of post-inoculation hepatitis. Those who served in the 1939–45 war will remember that inoculation parades certainly did not allow for a clean sterile syringe and needle for each person, and that "infective hepatitis" was one of the most serious and baffling medical problems of many formations—particularly perhaps of the Middle East Forces in 1942–43. Moreover, there was a higher incidence of this disease among officers, who were perhaps in general more conscientious than other ranks about keeping their inoculation programme up to date. ELLIS [1] showed that in Naval units there was a disproportionately high incidence of jaundice among those who had recently received typhoid-paratyphoid vaccine or tetanus toxoid. HOWELLS and KERR [2] and HUGHES [3] gave striking figures for the incidence of jaundice among those who had recently received penicillin without the benefit of a clean sterile syringe and needle. The practice now commonly adopted of fitting a clean sterile needle for each person to a syringe used for inoculating 5, 10, or 20 patients does not eliminate the risk of hepatitis and may even

1. Ellis, F. P. *J. Hyg., Camb.* 1953, **51**, 145.
2. Howells, L., Kerr, J. D. O. *Lancet*, 1946, i, 51.
3. Hughes, R. R. *Brit. med. J.* 1946, ii, 685.

increase it; for EVANS and SPOONER [4] showed that the small amount of fluid which always enters a needle in the tissues will be aspirated on to the nozzle of the syringe when the needle is taken off. In this way the whole contents of the syringe are likely to become infected.

The unmeasured risk of post-inoculation hepatitis can be eliminated only by providing a separate sterile syringe and needle for each person inoculated, as was recommended as the right procedure by an authoritative group of experts on immunisation which met in London last year.[5] This is admittedly inconvenient: it means that inoculation clinics must be better organised with enough helpers to sterilise and load syringes or enough sterile syringes and needles prepared before the inoculations to allow one for each patient. Inevitably there will be a plea that the cost is prohibitive. The cost of the material inoculated will often be of the order of 3–5*s*. a dose, and the cost of sterilising needle and syringe of the order of 6*d*. or perhaps a little less.[6] The present ineffective and dangerous methods of preparing and using syringes and needles cost something, so the new cost involved is not so high a proportion of the total cost as may be feared. Moreover the cost of medical and nursing care of those with preventable hepatitis, though unknown (and chargeable to a different account) cannot be negligible. On the ground of cost, therefore, the guarantee of safety does not seem to be ruled out. Even now at least one enlightened public-health authority—Manchester—is providing a service of sterile syringes and needles.[7] Some authorities, on the other hand, have felt themselves bound by the recommendations of the Medical Research Council's War Memorandum (no. 15) on the *Sterilisation, Use, and Care of Syringes*, which was published as long ago as 1945. This memorandum, reasonable enough in the light of what was then known, suggested that mass inoculations might be done by changing the needle for each new patient but using the same syringe for more than one. The risk was recognised but was rated as one that "must be accepted". A working party of the Medical Research Council has now indicated in an official communication [8] that the next edition of the memorandum on sterilising syringes will certainly recommend the use of a separate sterile syringe and needle for each inoculation.

There is an overwhelming reason for acting now on this recommendation—namely, the strain placed on the consciences of those who have been aware of bad practice but have nevertheless kept silent owing to the argument that if they spoke out the certain effect would be a reduction in the numbers of children protected against poliomyelitis. Hepatitis is not invariably mild: it may be fatal, or it may leave the liver seriously damaged. There is no specific remedy. One consultant in the hospital service tells us of an illuminating episode affecting members of his family:

In October, 1958, the consultant, his wife, and their three children were all given the third of their doses of poliomyelitis vaccine. This was taken from a multiple-dose container and inoculated, through a separate clean sterile needle for each person, by means of a common syringe which had already been used on earlier patients. At the end of January, 1959, the wife and one of the children developed febrile illnesses with slight jaundice, liver enlargement, and bile in the urine. Because this episode affected a doctor's family the mild jaundice was observed and a relationship with the inoculation established. Happily the episode had no sequelæ; but how many similar ones are there?

This is an illness that can be prevented, and should be. In our view parents have every right to demand protection for their children against this risk, and doctors have a clear duty to provide it. Indeed we believe that doctors should, if necessary, make public their protests against any continued pursuit of a practice which is now well known to be wrong. In clinics the boiling of many syringes and needles calls for much organisation. In general, we believe that boiling will be found less practicable, and no cheaper, than the use of dry sterile syringes prepared beforehand. Dry-heat sterilisation is preferable because by this method the syringe and needle can be sterilised fully assembled, lubricated, and sealed in a metal container. The plastic disposable syringe and needle is an attractive proposition, but the methods of sterilising such syringes require some further study.

Loss of Serum-proteins into the Intestine

ABOUT twelve months ago GORDON [1] and SCHWARTZ and JARNUM [2] drew attention to the condition in which hypoproteinæmia is brought about by loss of serum-proteins into the small intestine. At that time we pointed out that this syndrome of "protein-losing gastroenteropathy" must be added to the list of possible causes of generalised œdema associated with low serum-albumin levels. In 1949 ALBRIGHT et al.[4] found that hypoproteinæmia could be due to rapid disappearance of proteins from the plasma; they administered normal human serum-albumin to the patients, and by measuring nitrogen excretion demonstrated increased albumin catabolism. Others using the method of injecting serum-albumin labelled with ^{131}I showed that in hypertrophic gastritis the labelled serum-albumin was lost into the stomach, and in ulcerative colitis and regional enteritis it was lost into the intestine; but the available techniques did not enable the loss to be estimated quantitatively. GORDON [1] prepared a polyvinylpyrrolidone (P.V.P.) labelled with ^{131}I; and this plasma-protein substitute, injected intravenously, found its way into the gastrointestinal tract, was excreted with the fæces, and could there be readily estimated. He showed that up to 1·5% of a dose appeared in the fæces of healthy persons. Patients with hypoproteinæmia due to

4. Evans, R. J., Spooner, E. T. C. *ibid.* 1950, ii, 185.
5. A Symposium on Immunization in Childhood. Edinburgh, 1960.
6. The Planning and Organization of Central Syringe Services. London, 1957.
7. See *Lancet*, 1959, ii, 405.
8. *Mon. Bull. Minist. Hlth Lab. Serv.* 1960, **19**, 26.

1. Gordon, R. *Lancet*, 1959, i, 325.
2. Schwartz, M., Jarnum, S. *ibid.* p. 327.
3. *ibid.* pp. 351, 1106.
4. Albright, F., Bartter, F. C., Forbes, A. P. *Trans. Ass. Amer. Phycns*, 1949, **62**, 204.

nephrosis or hepatic disease, or associated with advanced malignancy, showed no increased excretion of the labelled P.V.P. The test was carried out on 9 patients with " hypercatabolic hypoproteinæmia "; these patients were young adults and children whose main symptom was dependent œdema. They had previously been found to have abnormally rapid loss of labelled serum-albumin, and they showed considerably increased excretion of labelled P.V.P., varying from about 2 to 10% (in 1 case 20%); the increased P.V.P. excretion was roughly correlated with the fall in serum-albumin level. SCHWARTZ and JARNUM [2] used GORDON's labelled P.V.P. to test the permeability of the gastrointestinal tract in 4 more patients with œdema, low serum-albumin, and rapid degradation of labelled albumin. They all showed increased P.V.P. excretion—about 3–5 times normal. 1 patient had no obvious lesion of the gastrointestinal tract; 1 was found at laparotomy to have widespread pigmentation of the small intestine involving the muscular but not the mucous coats; 2 had hypertrophic gastritis. Of these 2, 1 died after partial gastrectomy; but the other survived, and a month after the operation his serum-albumin was nearly normal, his labelled P.V.P. excretion was quite normal, and his œdema had disappeared. Increased P.V.P. excretion was also found in 3 patients with cancer of the stomach and 1 with steatorrhœa.

HOLMAN et al.[5] have now reported studies on 6 patients with this idiopathic hypoproteinæmia and œdema who all showed rapid disappearance from the plasma of labelled serum albumin and γ-globulin; in 3 intestinal lesions developed later. 1 of these patients had had œdema and hypoproteinæmia for nineteen years before a mass appeared in the left upper quadrant of the abdomen; rapid disappearance of labelled serum albumin and γ-globulin had been demonstrated. An exploratory operation showed dilated and stenotic loops of jejunum and a thickened friable mesentery; resection was judged to be dangerous, but biopsy specimens of mesenteric nodes were taken and showed a non-caseating granuloma. This patient was treated with 10 mg. prednisone daily, which controlled the œdema. In the 2nd case œdema and diarrhœa had developed at the age of 14, and hypoproteinæmia was found; labelled serum-proteins disappeared with typical rapidity. Three years later an abdominal mass was explored and was found to consist of fixed proximal jejunum in " a retroperitoneal mesenteric mass ". Biopsy showed acute and chronic inflammatory changes in the mass but only œdema of the mucosal wall in the jejunum. At this stage resection was not attempted, but in the next year perforation of the affected jejunum made this necessary. After the resection all the signs and symptoms disappeared and the serum albumin and γ-globulin levels returned to normal. The 3rd patient was a child of 4; at the age of 3 years splenectomy had been performed on account of cyclic neutropenia. The reasons for admission were fever, emaciation, and buccal ulceration. Low serum-albumin and γ-globulin levels were found and these proteins disappeared rapidly from the plasma when injected. Eventually the occurrence of melæna led to laparotomy, at which multiple ulcers in the terminal ileum and ascending colon together with an infiltrative lesion of the gut wall extending into the mesentery were found. The microscopic findings were non-specific. After resection of the affected bowel the patient recovered and normal growth was resumed; his serum-albumin became normal, but the γ-globulin remained low.

HOLMAN et al.[5] have made interesting observations on the fate of labelled serum-proteins by collecting samples of jejunal fluid from patients with this protein-losing gastroenteropathy. When the fluid is fresh 60% of the radioactivity is bound to protein, but after thirty minutes at 37°C it is no longer bound. It is known that after intravenous administration of ^{131}I-labelled proteins, the radioactive isotope appears in the urine. HOLMAN et al. suggest that, when serum-proteins pass into the intestine, they are digested by the intestinal enzymes; the ^{131}I is reabsorbed from the intestine and excreted in the urine. By immunological methods they showed that serum-proteins are contained also in normal intestinal secretions; hence the protein-losing gastro-enteropathies represent a quantitative rather than a qualitative abnormality. They point out that diarrhœa when present might account for the loss of serum-protein from the body via the stools; but in some patients there is no diarrhœa, and they suggest that the hypoproteinæmia may depend on failure to reabsorb and resynthesise the breakdown products of the serum-proteins lost into the intestinal juices and there digested. Such a failure is already known to occur in nephrosis. HOLMAN et al. have made some admittedly approximate calculations of the total body-albumin synthesis in their patients, and the figures show no appreciable difference from the normal.

The syndrome of protein-losing gastroenteropathy is thus more complex than it first appeared. It is established that in this syndrome serum-proteins disappear from the serum more rapidly than normal; the serum-proteins can be found in the intestinal fluids and are digested by the enzymes present. The daily resynthesis of albumin probably remains normal. The onset of the syndrome may eventually be followed by clear evidence of local non-specific inflammatory disease in the intestine, and in 2 patients hypoproteinæmia and œdema disappeared after resection of the diseased bowel. But HOLMAN et al. are not convinced that the actual loss of serum-protein via the intestine is always greater than normal, and they believe that " more effective technics will be necessary in order to establish that excessive loss of protein into the intestine occurs, and to determine whether this is the sole abnormality, or whether abnormalities of digestion, absorption, or synthesis of protein also exist ". This work does, however, show how the use of new methods is extending our knowledge of the normal and abnormal function of the small intestine—an extension already pointing the way to better treatment for at least one syndrome.

5. Holman, H., Nickel, W. F., Jr., Sleisinger, M. H. *Amer. J. Med.* 1959, **27**, 963.

Annotations

COLLEGE OF GENERAL PRACTITIONERS: AN APPEAL

THE College of General Practitioners has never been short of good ideas or enthusiastic support; but in many enterprises invention and enthusiasm are too often restrained because there is not enough money to apply them effectively. And so it is now with the College, whose affairs have expanded prodigiously in the past few years. This rapid advance in the work and influence of the College in many countries calls for increased financial support, and the College council decided that nothing short of the establishment of a substantial endowment fund would meet the situation. The appeal made public this week aims at £1 million, "to build and equip a permanent home, to endow its educational activities and to establish a separately administered Research Foundation".

The College has been considering several sites in London for its new home. The cost of building and equipping the headquarters has been put at £450,000, and in view of this capital cost the College has not proceeded with these or other negotiations until adequate resources have been secured.

A second objective is to widen the scope of the College's educational work, both undergraduate and postgraduate. To give students and young doctors from all medical schools more opportunity to study at first hand diseases which seldom bring patients to hospital, and to maintain and extend the help offered to established practitioners, will need some £250,000 as endowment.

Finally, the most vital item in the College's plans is its research programme. It is proposed to establish a research foundation endowed with a capital sum to be invested and administered by a board of trustees who will receive money upon trust to assist the work of the College's research committee in promoting general-practitioner research. The foundation will be a separate entity and its trustees will be independent of the research committee. For this purpose, £300,000 is needed.

The appeal is made publicly for the first time this week, but over £250,000 has already been raised in the past few months by direct appeal to organisations and individuals. This good start is a tribute to the prestige which the College has won for itself in its short but useful career.

A brochure describing the appeal and how to respond to it may be had from the College at 41, Cadogan Gardens, Sloane Square, London, S.W.3.

CHOICE OF ANTISTAPHYLOCOCCAL AGENT

WHEN called on to treat a severe staphylococcal infection, the clinician wisely turns to the laboratory for guidance in the choice of antibiotic. The results of in-vitro sensitivity tests, although not infallible, may at least determine the short list. A hospital-acquired staphylococcal infection will probably be unresponsive to penicillin and the tetracyclines and possibly also to erythromycin. If this is so, oleandomycin is also precluded because of its cross-resistance with erythromycin. The toxicity of neomycin prevents its general use, and streptomycin is far less effective than kanamycin. The choice is therefore narrowed to four predominantly bactericidal drugs (vancomycin, kanamycin, ristocetin, bacitracin) and two predominantly bacteriostatic agents (chloramphenicol, novobiocin). Bactericidal antibiotics are generally considered preferable to bacteriostatic agents if a serious infection is to be eliminated in a debilitated patient with poor resistance. For this reason chloramphenicol and novobiocin have often been relegated to the position of one member of a combination of antibiotics. Of the four remaining bactericidal members of the short list, bacitracin is the least effective for a grave staphylococcal infection, so the final choice may lie between vancomycin, kanamycin, and ristocetin. Since there are no controlled trials to define the relative superiority of any one, other factors such as cross-resistance and toxicity may influence the final decision. Even national pride may play a small part, for the birth soils of these three antibiotics are indeed diverse. A soil sample submitted by a missionary in Indonesia yielded *Streptomyces orientalis*, from which vancomycin was produced [1]; *Streptomyces kanamyceticus*, yielding kanamycin, was isolated from soil in Nagano, Japan [2]; and *Nocardia lurida*, which provided ristocetin, comes from soil collected in the Garden of the Gods, Colorado Springs.[3]

Kirby et al.[4] have found vancomycin highly effective in the treatment of penicillin-resistant staphylococcal infections, and recommend its use for several reasons. It has relatively few side-effects, and a strain of staphylococcus resistant to it has not yet developed in any patient. The fact that it must be administered intravenously for systemic infections may be a limitation, but this route ensures high concentrations in blood and tissues. Furthermore, Kirby et al. have observed satisfactory responses to vancomycin in patients who had failed to improve with bacteriostatic antibiotics to which organisms were susceptible—which underlines the advantage of a bactericidal drug. Of a series of 33 patients with staphylococcal septicæmia, nearly two-thirds were cured. Since in some of the failures the patient died within the first twenty-four hours of treatment or because of serious underlying disease, the response to vancomycin alone may be counted gratifying; and the survival-rate compares favourably with that following treatment with combinations of other antibiotics. Vancomycin was administered intravenously in 1 g. doses twelve-hourly for about a fortnight. Occasional rigors, fever, and rashes (possibly due to vancomycin's high molecular weight) were controlled by intravenous hydrocortisone without discontinuing the antibiotic. Nephrotoxicity was never observed, but vancomycin possibly contributed to deafness in 1 patient.

In nearly a third of this large series of cases of staphylococcal septicæmia the source of infection was an indwelling intravenous polyethylene catheter—a source likewise responsible in the well-documented case reported by Dr. I. R. Wallace and Dr. N. A. J. Carson on p. 519 of this issue. They resorted to vancomycin when erythromycin and chloramphenicol had failed to produce clinical improvement and the infecting organism was adjudged resistant to most other antibiotics. They succeeded in controlling the infection in their patient—a uræmic child—without aggravating renal failure or producing irreversible deafness under circumstances in which ototoxicity is known to arise. Satisfactory control of dosage was achieved by repeated estimation of serum-vancomycin levels. The method of management described by Wallace and Carson will undoubtedly provide a pattern for others.

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2. Umezawa, H. *Ann. N.Y. Acad. Sci.* 1958, **76**, 20.
3. Grundy, W. E., Sinclair, A. C., Theriault, R. J., Goldstein, A. W., Rickher, C. J., Warren, H. B., Jr., Oliver, T. J., Sylvester, J. C. Antibiotics Annual 1956–57; p. 687. New York, 1957.
4. Kirby, W. M. M., Perry, D. M., Bauer, A. W. *New Engl. J. Med.* 1960, **262**, 49.

ALCOHOLIC CARDIOMYOPATHY

ALCOHOLISM is seldom considered as a cause of heart-disease; but according to Evans [1] alcoholic cardiomyopathy is commoner than is generally supposed, for the symptoms and signs are all too easily attributed to ischæmic heart-disease, and alcoholics usually prefer to remain anonymous even to their own doctors. Evans [1] has reported 20 cases in which certain electrocardiographic changes first led to the correct diagnosis; and he suggests that careful attention to the electrocardiogram will aid early recognition. In 17 of his patients abnormalities were confined to the T wave, and were usually found in lead I and the left ventricular leads. Evans describes three main types of change which he regards as characteristic of the condition, and each may occur alone or in combination with others in different leads. The commonest, found in 8 cases, was the dimple T wave, consisting of a shallow dimple-like depression replacing the normal T wave: it was originally described by Evans [2] as a feature of alcoholism in 1954, and has also been reported as a transient change following a meal in healthy young adults.[3] A low T wave with a cleft at its summit—the cloven T wave—was found in 7 cases and was associated with auricular fibrillation in 2, being unobscured by the arrhythmia in the absence of digitalis therapy. Spinous T waves, consisting of sharply pointed, though not necessarily tall, waves, were found in 2 cases; these can be distinguished from the tall peaked T waves sometimes seen in early cardiac infarction by their rather narrower base. In 3 cases blunt T waves were noted, but these were always associated with either a dimple or a cloven T wave in some other lead.

While regarding these changes as distinctive of alcoholic cardiomyopathy, Evans concedes that a dimple T wave might possibly result from localised cardiac infarction, and that a spinous T wave might be associated with ischæmic heart-disease—though so far he has not encountered such a case. Blunt T waves were previously reported by Evans and McRae [4] as a sign of limited infarction in patients with cardiac pain. Less specific changes suggesting the diagnosis are auricular fibrillation in the absence of any of the usual causes, and extrasystoles which are frequent, multifocal, and associated with moderate tachycardia: such extrasystoles occurred in 9 of the 20 cases. Paroxysmal auricular tachycardia and transient bundle-branch block were each found twice. Characteristic T-wave deformities usually accompany these less specific abnormalities, but in 3 cases extrasystoles occurred alone.

The clinical picture was seldom striking. Of the 20 patients 10 complained of breathlessness, and 6 of chest pain which was quite unlike cardiac pain in site, character, or relation to exercise. Palpitation and sweating were occasional symptoms. Often the patient had been referred for an explanation of his general unfitness. Physical examination was likewise unhelpful unless tachycardia or frequent extrasystoles raised the possibility of alcoholism. All 20 were well nourished, and 14 were frankly overweight. Heavy drinking was common to all, each patient having taken at least half a bottle of spirits daily for from four to twenty years. By contrast only 1 patient smoked excessively, and the majority smoked in moderation.

The early diagnosis of alcoholic cardiomyopathy depends, not only on correct interpretation of the electrocardiogram, but also on realisation that the clinical manifestations need not be similar to those of Oriental beriberi with the classical signs of high-output failure—a point emphasised by Weiss and Wilkins [5] and later by Brigden.[6] Heavy drinking is seldom admitted spontaneously; and, once the suspicion has been aroused, confirmation must be most persistently sought from the patient's wife or family doctor. The correct diagnosis is literally vital; for early recognition followed by abstinence leads to complete recovery, whereas continued drinking may cause what Evans terms "complicated alcoholic cardiomyopathy" with intractable heart-failure resembling the high-output type—the end-result in 2 patients who did not heed his warning. The electrocardiographic changes described by Evans are admittedly subtle but are worth studying, for the results of treatment make the early diagnosis of alcoholic cardiomyopathy most rewarding.

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2. Evans, W. Cardiography. London, 1954.
3. Sears, G. A., Manning, G. W. *Amer. Heart J.* 1958, **56**, 591.
4. Evans, W., McCrae, C. *Brit. Heart J.* 1952, **14**, 429.
5. Weiss, S., Wilkins, R. W. *Ann. intern. Med.* 1937, **11**, 104.
6. Brigden, W. *Lancet*, 1957, ii, 1179, 1243.

THE CHARITIES BILL

THE practice of charity—caring for others—has for centuries been an important feature of English life. Medicine, education, and the relief of poverty have all depended to a remarkable degree on private benefactions. Even today, when so many social and educational services are financed by the State or local authorities, private charity (whether by past inheritance or contemporary gift) still continues. The range of charitable trusts recognised by the Law extends far beyond education and social welfare; Churches, learned societies, research organisations, and bodies sponsoring such causes as town and country planning are all included.

The importance of charity in this wider sense is emphasised by the protection and encouragement afforded by Parliament and the courts of law. For centuries the courts have been zealous to see that moneys given on charitable trusts are administered in accordance with the intentions of the donors. In the middle of the last century Parliament set up the Charity Commissioners as a Government department to supervise these trusts. Charities also have many financial privileges—they are not liable to income-tax, they are entitled to recover income-tax on subscriptions paid to them under deed of covenant, and they are often relieved of burdens imposed on other property owners.

Despite these advantages, most charities have faced serious difficulties since the war. Inflation has reduced the value of income from endowments, and inflation and high taxation have gradually dried up many sources from which support used to come. Changing circumstances have sometimes rendered the objects set out in the trust deed obsolete or at least obsolescent, yet the courts and the Charity Commissioners have only limited powers to amend the objects of a trust.

Against this background, in 1950 the then Prime Minister appointed a committee, with Lord Nathan as chairman, to consider changes in law and practice which would enable the community to derive most benefit from its charities. The committee reported in 1952, and its main recommendations were:

The jurisdiction of the Charity Commissioners and the Ministry of Education should be strengthened.

Up-to-date classified records to help would-be beneficiaries and voluntary workers should be compiled by the Commissioners and the Ministry.

Trustees should be allowed to invest in equity shares quoted on the Stock Exchange.

The definition of charity (at present contained in an Act of 1603) should be reworded.

The Commissioners and the High Court should be given wider powers to alter trusts to meet "the spirit of the intention of the founders" or for other reasons, and a local authority should have the power to make proposals for any trust in its area.

Charities should be allowed to cooperate with local authorities to further work of interest to both.

At last action is being taken to give effect to most of these recommendations. The Charities Bill, presented by the Lord Chancellor last month, provides for the registration of charities, specifies the circumstances in which the objects of a trust may be changed, and provides a statutory foundation for cooperation between charities and the statutory welfare services. (The proposal that trustees should be able to invest in commercial equities is being dealt with in another Bill.)

The new Bill does not, however, permit a local authority to propose schemes for the alteration of charities; but a local authority may, if the trustees agree, review the working of any charity (other than an ecclesiastical charity) in its area and report to the Commissioners. Nor does the Bill attempt a new definition of charity. This is perhaps understandable, for another, early-17th-century, definition of charity, contained in the Authorised Version of the Bible, is still in use.

HÆMATOGENOUS OSTEOMYELITIS

In childhood hæmatogenous osteomyelitis is usually caused by staphylococcal infection; the organism gains access via the nutrient artery, with consequent acute inflammation in the metaphyseal region. Injection of the blood-vessels [1] confirms the accepted view that the likely reason for this localisation is the anatomy of the small vessels in this region. The main vessels split up into capillaries which at the metaphysis turn through 180° and enter venous sinusoids; and these form an ideal situation for the organisms to take root. There is no connection between the metaphyseal and epiphyseal vessels after the age of 1 year; so in childhood the infection does not usually involve a joint and the growth mechanism is rarely damaged—though it may be overstimulated. In infancy—i.e., before the age of 1 year—there is no such barrier and the metaphyseal vessels extend into the epiphysis. At this age the infecting organism is sometimes a streptococcus, which, because of the vascular arrangement, will not be confined to the metaphysis alone but will extend to the epiphysis; the joint will be involved and deformity may result from damage to the growing epiphysis.

In adults osteomyelitis of the long bones is comparatively rare. It is more commonly found in short, flat bones of the spine or pelvis. When the long bones are affected the joints are commonly involved because, when growth ceases and the epiphyseal cartilage is obliterated, vessels once more extend from the metaphysis into the epiphysis so that infection in the former readily spreads to the latter. The infection also spreads rapidly along the shaft; but extensive sequestration is uncommon, and instead irregular atrophy with limited involucrum formation results. In the spine the area of destruction begins in the metaphysis of one vertebra and spreads to its neighbour in the next vertebra. Vascular injections by Wiley and Trueta [2] suggest that this spread is determined by the arterial arrangement within and around the vertebræ, and is unrelated to the venous network. They could find no evidence of direct spread from the pelvis to the spine.

Penicillin revolutionised the treatment of acute osteomyelitis, the mortality of which has now been reduced to a fraction of 1%. The cause of the formerly high mortality was septicæmia, which precedes the bone infection; but this infection, though less dangerous to life than the septicæmia, is sometimes associated with lengthy invalidism with life-long recurrences.

Treatment of the local bone disease has been much debated. Before penicillin, discussion revolved around early or delayed operation, and extensive guttering of bone or just incision of abscesses and drilling. The introduction of penicillin caused the discussion to take a somewhat different turn. Is operation necessary at all? Should abscesses be left alone, aspirated and washed out, or incised and the bone drilled? Sometimes the infection will resolve completely without operation, provided the dosage of penicillin is adequate. Trueta and Morgan [3] recommend 1 million units daily divided into three-hourly doses. In more advanced cases the problem is more difficult. Leveuf [4] considered that the infection caused thrombosis of the nutrient artery which resulted in sequestration; and for this reason he did not believe that there was any value in early operation. Higgins et al.[5] thought that stripping of the periosteum and thrombosis in the vessels was the danger. They recommended that the abscess be aspirated, if necessarily repeatedly, the cavity being washed out and filled with penicillin. This, they said, was preferable to open operation with the risks of secondary infection. Agerholm and Trueta,[6] on the other hand, held that tension within the bone preceded the thrombosis, and that if the condition did not respond to antibiotic treatment within twenty-four hours, the abscess should be incised and the cortex of the bone drilled in the metaphysis, and if necessary the diaphysis, to relieve the internal pressure and evacuate any pus; the wound could safely be sutured at once. In 1954 Trueta and Morgan [3] reviewed the first 100 patients treated in this way: in 66, anatomical restitution in the bone was complete. It has become increasingly clear that the risks of early operation are small compared with the benefits to be gained from it in the prevention of chronic osteitis and sequestration. But a new problem has arisen: the infecting organism—usually a staphylococcus—is increasingly often insensitive to the older antibiotics. Fortunately it commonly responds to one of the new antibiotics.

The outlook has not improved similarly in chronic osteomyelitis, where the infection is usually mixed and the organisms are deep-seated in sclerotic bone and scar tissue, well protected from antibiotics. Rowling [7] emphasises that not only the bone but also the periosteum, muscle, and even skin may be involved; and for treatment to be successful all scar tissue must be excised completely, whichever tissue may be involved. This may leave a large bone defect. If the raw area is covered with free skin grafts a thin unstable scar will result which may break down. It is better to fill the defect with viable tissue, such as a muscle belly, in which blood and nerve-supply have been preserved intact. If no muscle is available, rotation or cross-leg flaps may be used.

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Public Health

PARATHION POISONING FROM CONTAMINATED BARLEY

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WITH the increasing use of toxic organo-phosphate compounds as agricultural insecticides, the recognition of the toxic symptoms and knowledge of the correct antidote become increasingly important. Organo-phosphates inactivate cholinesterase, with resulting accumulation of acetylcholine which causes the toxic symptoms. In September, 1959, an explosive outbreak of poisoning from barley contaminated with 'Parathion' (*O,O*-diethyl-*O*-*p*-nitrophenyl phosphorothionate) occurred in Singapore; in all, 35 children and 3 adults were affected and 9 children died. This is the first known outbreak of parathion poisoning in Singapore.

The first intimation of the trouble, on Sept. 6, was the admission in rapid succession to the general hospital between 4 P.M. and midnight of children obviously suffering from the effect of some poison or toxin. In all, 13 children and 1 adult were admitted that evening and 1 child was brought in dead. 8 children were in coma on admission or rapidly went into coma; and, of these, 4 died. On questioning the parents, the common factor was undoubtedly barley, which had been bought by all from a single shop. The common method of preparing it was to wash the barley three or four times and then boil in water for about an hour; about 1 cupful of barley to 4 pints of water was used. The clinical features varied according to the amount eaten, but the sequence of events followed much the same pattern. From fifteen minutes to two and a half hours after consuming the barley or barley-water the child felt discomfort in the abdomen, usually vomited, and rapidly went into a pale collapsed state often slipping quickly into coma. In the severe cases the onset was so sudden that the children fell in collapse and coma. There was sweating, excessive salivation, and increased secretions in the lungs, and in some cases muscle twitching was noticed. At first the pupils were dilated but later became pinpoint. This latter sign indicated a possible parasympathetic stimulant, so without delay large doses of atropine were given with dramatic results. The excessive secretions in the lungs rapidly cleared and consciousness slowly improved over a period of hours. After this all cases received atropine immediately on admission, and only 3 patients died after adequate treatment had been given. At this stage an organo-phosphate compound was suspected.

Clinical Features

Altogether 53 people were involved; 13 had severe symptoms, 25 had mild symptoms, and 15 had no symptoms (table I). Table I also shows the numbers in each of the different families who were involved in the outbreak.

TABLE I—THE FAMILIES

Family	No. of members involved	No. of cases according to severity		
		Severe	Mild	No symptoms
A	9	5	3	1
B	6	1	5	0
C	8	1	7	0
D	3	1	1	1
E	5	0	1	4
F	6	3	1	2
G	9	1	7	1
H	7	1	0	6
Total	53	13	25	15

There seemed to be a clear-cut difference in the clinical manifestations between the severe and the mild cases. In those with severe symptoms the commonest initial sign was sudden collapse, followed in a few seconds by deep coma with dyspnœa, sweating, and frothing in the mouth. Those with mild symptoms usually experienced abdominal discomfort accompanied by vomiting or diarrhœa and later had headache, giddiness, and malaise.

Collapse

This was sudden and was the first sign noticed in all the 13 severe cases, coming on very shortly after ingestion of the barley preparation. There seemed to have been no premonitory symptoms before the collapse. The time of onset of collapse varied from fifteen minutes to two and a half hours after eating the barley or barley water.

Fits

In about 50% of the severe cases the patients had fits which came on much later than the collapse. In one patient a lumbar puncture was done and the cerebrospinal fluid was not under increased pressure and was normal on biochemical and cytological examination. The fits could have been asphyxial fits due to the pulmonary œdema.

Sweating

In nearly all the severe cases this was noticed over the whole body, especially the face and extremities.

Dyspnœa

All the severe cases had dyspnœa, which was due to the accumulation of bronchial secretions. The most dramatic effect of atropine was the abolition of dyspnœa with the reduction of the bronchial secretions.

Pupils

In the majority the pupils were constricted and non-reactive to light, but in 3 of the severe cases the pupils were dilated prior to the administration of atropine and in one case (case 11) the pupils later became constricted despite repeated injections of atropine. This child subsequently died.

Blood-pressure

The blood-pressure was recorded in 4 of the severe cases, and in 3 of them there was slight hypertension; the 4th case (case 6) had hypotension. Among some of the mild cases there was also a slight rise in blood-pressure, and we gained the impression that parathion produces a rise in blood-pressure except at the stage of circulatory collapse due to severe cerebral depression, when the blood-pressure was very low.

Coma

In all the severe cases the patients were deeply unconscious following the collapse.

Muscle Fasciculation

This was sought in 6 of the 13 severe cases and was found in 5. It appeared most notably in the four extremities and tongue, and was about the last sign to disappear when the patient recovered after administration of atropine. In one patient (case 9) consciousness returned after two and a half hours but muscle fasciculation could still be seen twelve hours later. Fasciculation persisted longest in the muscles of the fingers and toes. Atropine does not prevent the direct effect of excessive acetylcholine on the muscle-fibres.

Chest

In all the severe cases in which the patient was admitted alive, moist sounds were heard over the lungs and were often accompanied by foam in the mouth.

Electrocardiographic Findings

Electrocardiograms (E.C.G.) were recorded in 5 patients, of whom all but 1 (case 26) had already been given atropine, and the salient features were as follows:

Case 26.—Mild case. No atropine given. ST depression of 1 mm. in leads III, V_1, and V_3.

Case 9.—Severe case. Atropine given.

(*a*) Child in coma 4: ST depression in all leads (up to 4 mm. in V_3) except lead III, and aV_R where there was elevation of the ST segment.

(*b*) Child in coma 1: disappearance of ST depression, but pronounced diminution in the P waves, the highest voltage corresponding to 1 mm.; T waves also diminished, of rounded contour and broad.

(*c*) After twelve hours, fully conscious: P waves more definite; T-wave voltage increased though tendency to remain broad and rounded persisted.

Case 45.—No symptoms. Atropine given. ST depression in all leads, except aVr where there was elevation of ST; T waves tended to be broad.

Case 11.—Severe case. Atropine given. ST depression pronounced in all leads, as much as 3 mm., especially in chest leads; T waves tended to be broad.

Case 30.—Mild case. Atropine given. There was no ST depression in the leads done (i.e., I, II, III, aVr, aV_L, and aV_F; chest leads were not done).

Serum Calcium and Inorganic Phosphates

These were estimated in only a few cases and were essentially normal:

Case 30.—Inorganic phosphate 4·1 mg. per 100 ml.

Case 45.—Calcium 9·7 mg. per 100 ml., inorganic phosphate 4·2 mg. per 100 ml.

Case 9.—Calcium 9·1 mg. per 100 ml., inorganic phosphate 2·9 mg. per 100 ml.

Delayed Onset

Case 13.—A 2-year-old female child took half a bowl of the liquid preparation fifty-six hours before symptoms of poisoning became manifest; and despite treatment the child died shortly after admission. The other 6 members of the family (table I, family H) also each partook of the same amount but suffered no ill effects. Necropsy on case 13 revealed considerable amounts of parathion in the mucous membrane of the alimentary tract. We are unable to explain the delayed onset of symptoms in this case and the fact that the other members of the family under the same circumstances suffered no ill effects.

Management

Atropine

When it was realised that the symptoms and signs could be due to organo-phosphate poisoning, atropine was given to those with severe or mild symptoms. The drug was given intramuscularly and in 2 patients it was administered intravenously, a single dose varying from gr. $^1/_{200}$ to gr. $^1/_{50}$ according to the patient's age and the severity of the symptoms. Successive doses were given in some patients; the intervals between doses in some cases were as short as fifteen minutes and in others as long as a few hours. The most dramatic effect of atropine was the reduction in the bronchial secretions and amelioration of dyspnœa, improvement being detected as soon as five to ten minutes after administration. In those who recovered, consciousness and blood-pressure gradually returned to normal; but the muscle fasciculations remained for a longer time.

Supportive Treatment

A stomach washout was done immediately with a wide-bore tube, and in many of the patients barley grains were recovered.

Some of the severe cases were intubated and the bronchial secretions aspirated through the endotracheal tube, and in those with respiratory failure oxygen was given through the tube and respiration maintained with the anæsthetic bag.

Broad-spectrum antibiotics were given to all patients with severe symptoms, in order to prevent the development of bronchopneumonia.

Pyridine-2-aldoxime methiodide (P.A.M.) or the methane sulphonate (P_2S) was not given as these drugs were not available in Singapore at the time.

Progress

Those who survived after having had severe symptoms were followed up carefully for several weeks, and were found to be perfectly healthy.

Representative Case-records

Case 6.—A healthy girl, aged 7 years, took one bowl of barley with grains at 5.30 P.M. on Sept. 6, 1959. At 8 P.M. she complained of epigastric pain, gave a loud cry, and collapsed with increased mucous discharging from her mouth. She was immediately brought to hospital and admitted at 8.25 P.M. On admission she was in coma 4, with cold and clammy skin. There was increased mucous discharge from her mouth and nose, and crepitations were heard from both lungs. Her pulse-rate was 140, regular, and blood-pressure 90/50 mm. Hg. Pupils were pinpoint and did not react to light. There was no gag reflex. All four limbs were flaccid, and deep tendon reflexes were absent, but fasciculation of the thigh muscles was noticed. Atropine gr. $^1/_{100}$ was injected intramuscularly at 10·30 P.M.; at 11 P.M. and 11.15 P.M. she was supported by oxygen tent and repeated suction. Within an hour the mucous discharge from mouth had diminished considerably and dyspnœa was less. The next morning the patient was conscious. The pupils were still pinpoint and lateral nystagmus was noticed. She also had visual hallucination and a fever of 104°F which subsided within twenty-four hours. Her limbs were not flaccid, and deep tendon reflexes could be elicited. Twenty-four hours after admission her pupils were back to normal size and reactive to light and she was rational. She had two more doses of atropine gr. $^1/_{100}$ on Sept. 7 at 8.30 A.M. and 2.30 P.M. Her progress in the next six weeks was uneventful.

Case 9.—A 7-year-old girl suddenly collapsed and became deeply unconscious an hour after ingesting the barley preparation. On examination she was in deep coma and sweating profusely. The pulse-rate was 100 and the blood-pressure 140/90 mm. Hg. The pupils were dilated but reacted sluggishly to light, and the fundi showed some arteriolar constriction. Muscular twitches were observed in all four limbs, face, and tongue. The deep reflexes in the limbs could not be elicited, and the plantar response was flexor. The chest was full of

crepitations. Atropine gr. $^1/_{50}$ was given intramuscularly at once and repeated at intervals—gr. $^1/_{100}$ fifteen minutes later and gr. $^1/_{100}$ intravenously two and a half hours later. The stomach was washed out with recovery of barley grains. An endotracheal tube was inserted and bronchial secretions were sucked out. Two and a half hours after admission the child showed signs of regaining consciousness, but she was unable to speak until twelve hours after admission. Fifteen minutes after the first dose of atropine the chest became dry, and excessive sweating ceased two and a half hours after treatment. The muscle twitches did not disappear till fourteen hours later. The blood-pressure became normal three hours after the first dose of atropine. There was ST depression in nearly all leads in the E.C.G., which became normal three hours afterwards. The child was subsequently followed up as an outpatient for several weeks, and her recovery was complete.

Case 10.—The 5-year-old brother of case 9 took $1^1/_2$ bowls of the barley preparation at 7.30 A.M. on Sept. 7 and forty minutes later suddenly collapsed without any premonitory symptoms. The mother found him deeply unconscious and sweating profusely, and he was also dyspnœic and foaming at the mouth. He reached the hospital thirty minutes later still in coma with dyspnœa and foam in the mouth. He had fasciculation of the muscles of all limbs, with generalised fits; the pupils were dilated and there were massive crepitations in both lungs. In a few minutes the patient died.

Postmortem Findings

All patients who died were examined at necropsy and the findings were fairly uniform. There was cyanosis of lips, fingers, and toes. *Œsophagus:* the mucosa was congested. *Stomach:* the mucosa was congested with patches of hæmorrhage, and in most cases barley grains were seen; microscopically, dilated blood-vessels were seen in the mucosa and submucosa. *Intestine:* patchy areas of hyperæmia were observed. *Heart:* the heart and great vessels were normal. *Lungs:* some subpleural petechiæ were seen, and the cut surface showed gross congestion with excessive œdema fluid which flowed freely; microscopically, the vessels were grossly congested, the alveolar walls were thickened, and the alveoli were filled with œdema fluid. *Liver, spleen, and kidneys:* there was moderate congestion, and microscopically the liver showed accumulation of lymphocytes around the portal tracts and along the interlobular septæ. *Brain and meninges:* the meninges were normal; but the brain was œdematous and microscopic examination revealed vascular congestion in the cerebrum, basal ganglia, and pons.

The findings were not specific but showed the usual local signs of inflammation in the alimentary tract, and the signs of asphyxia due to increased bronchial secretions and pulmonary œdema.

Epidemiology and Control

In all the cases admitted on the first day certain features were significant: (1) all gave a history of having taken barley; (2) many members of a family, nearly all children, were affected; (3) all the cases came from the Queenstown area. The clinical picture of poisoning by a powerful anticholinesterase agent pointed to one of the organophosphate insecticides. The vehicle through which the poison was transmitted appeared to be barley. Subsequent investigations confirmed both these points.

" *Barley-poisoning* " *Made Notifiable*

The following morning (Sept. 7) by administrative instruction every case of suspected " barley-poisoning " was made notifiable to the medical superintendent of the General Hospital, who was required to transmit the information to the health authorities immediately for investigation. 47 cases admitted to hospital were so notified during the outbreak (table II).

Breaking the Chain

As soon as it was established that barley was the most probable vehicle by which the poison was being transmitted it was decided to take the important step of making the public stop taking any more barley. By the morning of Sept. 7 (sixteen hours after the first case was admitted) it was apparent that cases were not confined to any one area. A full statement on the outbreak was issued by the Ministry of Health at noon; the public were advised not

TABLE II—" BARLEY-POISONING " CASES

Date	Total cases notified (all admitted)	Admitted confirmed cases		Mild poisoning found among admitted cases	Total cases	Deaths
		Severe	Mild			
Sept. 6	18	9	9	15	33	6
" 7	14	3	1	..	4	2
" 8	8	1	..	..	1	1
" 9	5	..	..	..	..	..
" 10	1	..	..	..	..	..
Oct. 1	1	..	..	..	..	..
Totals	47	13	10	15	38	9

to take barley in any form until the investigations were completed. The announcement was given wide publicity and radio broadcasts were interrupted every 15 minutes to repeat it. Vans fitted with loudspeakers toured the Queenstown area, from which most of the cases came. The statement was published in all local newspapers. The effect of the announcement was threefold:

1. Only 1 confirmed case of poisoning occurred after noon on Monday, Sept. 7, compared with 37 cases up to noon.

2. All cases admitted to hospital and notified as " barley-poisoning " up to noon were confirmed cases, but 23 out of the 24 cases admitted and notified after the announcement were not confirmed. These cases were the result of a rush to hospital by apprehensive persons who feared that they might be suffering from poisoning.

3. No person suspected of " barley-poisoning " gave a history of taking barley after Sept. 7.

Toxicological Investigations

Close collaboration with the chemists was maintained throughout. All material (e.g., remains of food taken, barley in households or shops, and postmortem specimens) was submitted for analysis. The toxic agent was identified by them as *O,O*-diethyl-*O*-*p*-nitrophenyl phosphorothionate (parathion), a highly toxic agricultural insecticide.

One bag of barley taken from a shop in Queenstown accounted for 29 of the 38 cases and for 7 of the 9 deaths. Analysis showed that concentrations of the parathion varied in different parts of this bag (from 1·8 to 0·44% w/w). The paper lining of the gunny bag showed concentrations of 3·3% at the top end and 0·15% at the lower end. The concentration of the parathion in the barley in this bag was 0·18%.

Another contaminated bag of barley found in another shop in the town contained 0·044% of parathion.

Reports from the health authorities in the Federation of Malaya established that bags of contaminated barley were found in two towns there.

Quantitative analysis of a sample of the left-over cooked barley showed that the parathion content was 6 mg. in 534 g. of barley and water. Although the uncooked barley was found to contain as much as 1800 mg. of parathion per kg., the amount in the cooked barley would be considerably less because of washing and cooking.

Field Investigations

District health officers and public-health inspectors of the local health authorities carried out the field investigations. The main lines of investigation were:

1. A check on the story given by *the patient* to the hospital authorities, including detailed information regarding the onset and nature of illness, the meals taken, and others who took the same meals and their condition. Early in the investigation "barley" was suspected, and details of how the barley was prepared and consumed and the name and address of the retailer who sold the barley were obtained. Investigators collected all left-overs of the suspected meals, any other suspected foods, and remains of uncooked barley.

2. The *retailer's premises* in each case (there were 16 of them) were checked for their general condition, details of barley purchases and sales, conditions of storage of barley, and the sales and use of insecticides and/or other poisons. All stocks of barley in the retailers' shops were sealed. Information was obtained about the wholesaler from whom the retailer had obtained his barley.

3. At the *wholesale dealers* (there were 5 of them) the usual check on storage and poisons was made. Existing stocks were sealed and books checked for details of sales—both local sales and re-exports to the Federation of Malaya and Borneo. From details of local sales, further barley stocks were traced and sealed. Details of exports were sent to the health authorities in the Federation and Borneo.

4. The information from the wholesalers pointed to *one importer*. In all cases the evidence pointed to the barley having come from a particular consignment. The importer's warehouse was inspected and barley stocks were sealed. Details of local and export sales were obtained. The suspected consignment of 200 bags had been imported from a West European country by a cargo vessel on Aug. 22, 1959. The consignment was stacked with another consignment, also of 200 bags, from the same country imported three days earlier; it was therefore necessary to treat this latter consignment also as suspect.

5. Investigations of the discharge of the consignment in the harbour from the ship into lighters (barges) and its transhipment to the importer's warehouse ruled out contamination at this point of transit.

6. The full cargo manifest and the loading plan for the entire outward voyage of the ship were checked. Full details of the actual storage of the barley consignment in relation to other cargo in hold no. 1 were studied. The findings were not conclusive.

7. Investigations regarding the barley at its source in Western Europe and its storage and transport to the port of export were checked through the good offices of the consul of the country, who reported that there was no contamination at the source.

From these investigations, the general picture of the outbreak can be pieced together. Some bags of loose pearl barley imported from Western Europe on Aug. 22 by a cargo boat had become contaminated with parathion, which is not available in Singapore. The nature of contamination appeared to be spilling or other localised contact of the barley with some quantity of parathion. The widespread distribution of the bags in three towns established that contamination could not have occurred at local retailers or wholesalers. Contamination could only have occurred at a central source.

In view of the substantial interval between the import of the barley and the occurrence of cases, it has not been possible to establish conclusively the point at which contamination occurred. This must remain speculative.

Once the picture was pieced together, every effort was made to trace the 400 bags of barley from the two suspected consignments. Except for 3900 lb. (equivalent of 36 bags) sold loose locally this has been done. This quantity of 3900 lb. has possibly been sold to small retailers and to householders and, in all probability, has already been thrown away.

The barley sealed in shops was subsequently surrendered by the dealers and destroyed. The public were advised to throw away all loose barley in their possession; dealers with stocks the origin of which they did not know were asked to surrender these.

All imports of fresh loose barley into Singapore were stopped for nearly three months while local stocks of loose barley were checked. Only when the health authorities were reasonably satisfied that there was no contaminated barley were fresh stocks released into the local market.

Discussion

The most usual cause of poisoning by organo-phosphate compounds is accidental contamination during insecticidal spraying of plants, particularly rice. In Japan it has been estimated that over 6000 persons were affected over a five-year period (Hiraki and Namba 1957). The popularity of parathion as a suicidal poison is increasing, however, and a report from Finland (Toivonen et al. 1959) shows that deaths from suicide due to parathion increased from 1 in 1952 to 94 in 1957. Reported deaths due to parathion poisoning in Finland in 1957 totalled 105. It is rare for food to be accidentally contaminated except when in the vicinity of a spraying operation. For this reason the outbreak in Singapore was of particular interest.

The poisonous effect of the organo-phosphate compounds depends on their ability to phosphorylate cholinesterase. The inactivation of cholinesterase in the body results in the accumulation of acetylcholine. Atropine counteracts the muscarinic effects of acetylcholine and to a certain extent the central effects, but has no effect on the nicotinic action; therefore the muscle fasciculation continues despite administration of atropine. Pyridine-2-aldoxime methiodide (P.A.M.), introduced by Wilson and Ginsburg (1955), and the corresponding soluble methane sulphonate (P_2S), reactivate the cholinesterase and cause the symptoms of toxicity to subside rapidly. According to Hiraki and Namba (1957, 1958), in man all the symptoms subside: muscle fasciculation ceases, and the red-cell cholinesterase rises immediately; but the serum-cholinesterase takes two to three weeks to return to normal. The dose of P.A.M. given was 1–2 g. intravenously. It still appears to be advisable to give atropine as well. Davies et al. (1959) suggest the possible prophylactic oral administration of P_2S with atropine intramuscularly. In the present series P.A.M. was not available, so atropine was given.

Animal experiments suggest that in an adult human being 12–20 mg. of parathion is a lethal dose. In the present series the amount of parathion ingested appeared to be related to the severity of toxic symptoms. Those who only had the barley-water were less severely affected than those who consumed the barley grains, and the more that was consumed the more severely was the patient affected. Furthermore, as would be expected, the younger the child the more susceptible he was to toxic effects. It is difficult to assess how much parathion was absorbed in the fatal cases. In some of the left-over cooked barley the amount of parathion found was 6 mg. in 534 g. of barley and water. One cup of barley and water weighs about 300 g. and has a volume of 9 fl. oz. In the present series one chinese bowl of the mixture (vol. 6 oz.)

was fatal for children aged 5–6 years but not for 2 children aged 7 years. It can therefore be assumed that 6 oz. of the barley mixture, weighing approximately 200 g. and containing about 2 mg. of parathion, was fatal for children 5–6 years of age. This suggests that the lethal dose for man is about 0·1 mg. per kg. body-weight.

The immediate control measure of wide publicity to prevent the public from taking barley in any form effectively prevented further cases. This gave the health authorities time to carry out field investigations and seal off stocks of contaminated barley. The chemical findings were invaluable in establishing the causal agent. Qualitative and quantitative analyses suggest that the barley had been accidentally contaminated by spilling or other local contact. Rapid transmission of information to the Federation of Malaya prevented the occurrence of cases there, though bags of contaminated barley were found.

The outbreak was promptly ended by means of coordination between hospital, field workers, and chemists.

Conclusions and Summary

In an outbreak of accidental ' Parathion ' poisoning due to contamination of barley in Singapore in September, 1959, 35 children and 3 adults were affected, and 9 children died.

The symptoms varied from abdominal discomfort, nausea, and malaise to vomiting, pallor, and collapse, the patient often passing rapidly into coma with excessive salivation, dyspnœa, increased secretions in the lungs, and muscle twitching. The pupils were at first dilated and later constricted.

Only atropine was available as an antidote. It was given in large doses and repeated as required. In most cases there was considerable improvement within one hour; the bronchial secretions and dyspnœa subsided and consciousness was regained. Supportive treatment included stomach washout, oxygen therapy, aspiration of bronchial secretions, and in 1 case intubation with positive-pressure respiration. Broad-spectrum antibiotics were given to prevent bronchopneumonia.

To prevent further persons from ingesting the contaminated barley, warnings were given through loud-speaker vans and over the radio, with immediate success. Contamination of the loose barley with parathion was confined to one particular consignment of 200 bags imported from one ship; and one bag from one shop was responsible for 7 of the 9 deaths. Contamination of the barley after it left the importer's warehouse, and contamination in the country of source, were excluded. The affected consignment of barley and another, suspect, consignment were traced throughout Singapore, Malaya, and Borneo and were destroyed.

We are grateful to Dr. C. Elaine Field and Dr. Quah Quee Guan and the staff of the pædiatric unit, General Hospital, Singapore, for their advice and help; to Dr. A. Jackson and Dr. Lee Kum Tatt and the staff of the department of chemistry, Singapore, for analysis of the poison and advice on its chemical properties; to Dr. Ho Kok Kheong, of the pathology department, General Hospital, for the necropsy findings; and to the health officers and the staff of the Government and City health departments in Singapore for their assistance in the epidemiological investigations. Our thanks are due to the Director of Medical Services, Singapore, for permission to publish.

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Medicine and the Law

A Libel Action

IN an action for damages for libel brought by a former part-time almoner's clerk against a woman consultant in respect of a letter written by the consultant to the secretary of the hospital house committee, on the trial before a judge and jury, the jury found that the consultant had been actuated by malice when writing the letter and assessed damages at £450.

After the almoner's clerk had been employed for a number of years at a children's hospital she received a letter from the board of governors of the parent hospital dismissing her from her employment. She complained, and as a result it was decided that a commitee should be set up to hear her appeal. Before this committee met, at the request of the secretary of the house committee the consultant wrote a letter setting out reasons why she thought the appeal should be dismissed. This letter was the subject of the libel action, the almoner's clerk alleging that the consultant wrote it maliciously, knowing its contents to be untrue. It was agreed that it was written on an occasion of qualified privilege, and the consultant conceded that the words set out in the letter were defamatory in their ordinary meaning; the almoner's clerk also alleged that the consultant meant, and was understood to mean, that she (the clerk) had interfered in the advice given by the consultant to patients, had improperly advised parents of patients, had interfered with and attacked the consultant, and by reason of those matters was unfit to retain her office. The consultant denied that she had been malicious.

Mr. Justice HINCHCLIFFE, summing up, said that the defence of qualified privilege was destroyed if the almoner's clerk could prove malice, but before she could succeed she must satisfy the jury on a balance of probabilities that the consultant was actuated by some malice or indirect or improper motive when she wrote the letter. The question for the jury was whether there was any evidence on which they could rely that the consultant used the occasion of writing this letter to vent some spite, ill-will, animosity, or hatred of the almoner's clerk. The clerk's case was that the consultant had developed animosity towards her, and being determined to get rid of her had written the letter recklessly to make certain that she would be dismissed. That was a very grave allegation to make against the consultant. The consultant, on the other hand, had said that she honestly believed that what she wrote was the truth, and that her experience of the clerk was such that she could not have written in terms other than she did. The jury might think that the consultant was concentrating on the more important matters of life and death and her mind totally rejected less important matters, and that she was telling the truth when she said she could not remember trivial conversations with the clerk. The question was whether the consultant honestly believed in the truth of what she wrote.

On the verdict of the jury judgment was entered for the almoner's clerk.

Mawhinney *v.* Shelley—*Queen's Bench Division:* Hinchcliffe, *J.* and a jury, Feb. 12, 1960. Counsel and solicitors: Lewis Hawser, Q.C. (Calvert Smith & Sutcliffe); J. R. Cumming-Bruce (Hempsons).

E. CARYL-THOMAS
Barrister-at-Law.

In England Now

A Running Commentary by Peripatetic Correspondents

AMONG the trickiest of the problems which arise when you woo the goddess Research is the authorship of the great work when it is ready to be ossified in print. Of course, once upon a time there was no problem. Your chief was the author, and that was the end of the matter; and on the rare occasions when he conceded assistance from his junior to the extent of allowing a second name to appear under the title, there was only one rule of precedence. But now that democracy is rearing its ugly head, even in our hospitals, such a solution is unacceptable. Bright (of course) has had the idea, and collected the cases and done the work, but Woolley (as usual) has played his part nobly in the background, adding an indefinable something to the whole investigation; he cannot be left out. The solution seems obvious—Bright and Woolley. But what will the readers think? Either that Bright has been throwing his weight around, lording it over poor Woolley, pinching his ideas, exploiting his experience and not admitting his merits, or (even worse) that the two of them could not agree and lamely fell back upon the alphabet to fix the order. A deliberately inverse-alphabetical order is no better, for the readers (not knowing the protagonists) will miss the subtlety of this, and conclude, quite erroneously, that the junior is Bright and his chief Woolley.

The difficulties multiply as the number of contenders for the title increases. Nowadays the large cooperative study is in vogue, and bacteriologists, pathologists, anæsthetists, and social workers are all invading what was once the physician's or surgeon's undisputed preserve. I am at this moment "preparing" a report for some five or six investigators. The ninth draft is being typed and so I am giving some preliminary thought to the credits. I discussed the point judiciously with some of those concerned, but we could see no solution. We put it to McTavish, our statistician; he suggested that we might draw the names "oot of a hatt," partly (we know) because he knew such a reply was expected of him, but partly (we suspect) because this was the only way he saw any chance of heading the list himself. Each of us was more worried by the chance that we might end it. And then, quite suddenly, the answer came to me—and not one answer but two. It happened when one of my colleagues remarked disparagingly that old So-and-so always put a spoke in the wheel of any inquiry he was involved in. So I shall let *all* of them put in their spoke, and have their names printed like the arms of a starfish. Or, as an alternative, they could be printed round the rim of the wheel; this way, come to think of it, an editor could even accommodate those Transatlantic papers with fourteen or more authors, arranging them (by McTavish's method), in a neat border all the way round the first page, with those entertaining printers' emblems to separate one name from the next and add dignity, beauty even, to what might otherwise look like a leaf from a medical directory.

I've just had another thought, though—how would anyone refer to the paper? Well, why should I worry about that; after all, that's *their* problem.

* * *

I have been wearing dark glasses when out and about on the wintry streets, as I have just had an eye operation. It is a revealing experience. Most people do not notice and barge cheerfully into you, but some are extremely solicitous, almost going off the kerb in their anxiety to avoid a collision. A workman repairing the road grasped me by the arm and insisted on leading me round a heap of rubble, which I could see for myself, and shouting "That's right, Guv," at five-second intervals. Shouting at anyone who wears dark glasses is a common response, as though anyone unable to see clearly must be hard of hearing also.

When I did some household shopping, assistants counted out the change aloud into my hand and dear old ladies insisted on letting me precede them at the bacon counter. Everyone was delighted when I left a packet of coffee lying on the counter and a panting grocer's assistant called me back from the door.

Not only dear old ladies, either, showed sympathy. Two sweet young things, on two separate occasions, offered to see me across the road, quite guilelessly I believe. Dorothy Parker's immortal couplet, I felt, should be amended:

Men in dark glasses
Never make passes.

But my wife was not so convinced of the innocence of their motives. She said I looked thoroughly sinister in my dark glasses and that girls at the impressionable age would naturally be attracted by someone looking like a character in a horror film.

* * *

As it is over a year since the last follow-up report on my genealogical researches, I had better record my further progress. Strictly speaking, there has been no progress, but we cannot allow scientific journalism to be stultified by such mean considerations as that.

Try as I will, I am unable to trace my paternal ancestry beyond my great-great-grandfather who, it may be recalled, was a plumber in Penzance. So, mindful of the true spirit of fundamental research, I have rationalised myself out of that situation. You will, I am sure, agree, as soon as the point is made, that it is maternal descent that matters most, especially when it is exclusively Scottish. And I am happy to say that here I have succeeded in delving a whole generation farther back, and my great-great-great-grandfather turns out to have been a crofter in the Black Isle.

With origins as far apart as Cornwall and Cromarty, it is no wonder (says my Welsh-Irish wife) that I am torn with internal conflict. In her opinion it is only by settling on Tyneside and living a life of compromise that I have kept an overt schizophrenia at bay.

* * *

Fanned by cool gales from the ill-fitting bedroom window, I spent a restless night and it was daybreak before I dropped into a troubled sleep. And then I heard it, a distant sibilant whisper. It grew louder and more insistent and at length its full horrible meaning dawned on me. It was George Stephenson trying out the Rocket, of course, and there was I fast asleep on the track. The noise rose in a last crescendo of hiss and whistle, the engine bore down on me, its lights flickered and became steady and at the same time a thousand sheep, left by an unvigilant shepherd to graze unsafely on the line, suddenly started to bleat in unison "Baa-aa-aa".

I woke up and started scalding my throat with superheated tea from the cup which my wife had put into my shaking hands. "Won't it be wonderful waking up to a lovely cup of tea every morning," she said, gazing fondly on the tea-making machine which was my birthday present. "Yes, my dear," I managed dutifully to mumble between borborygmi.

* * *

BIG FISH IN A SMALL POND

Molecules from enzymes stem
By catalytic processes;
And enzymes, what's the source of them?
Why genes, upon the best hypothesis.

So little rings and chains require
Enzymes to synthesise 'em
And genes, which stand a level higher,
Make enzymes and despise 'em.

But molecules feel sore about
The enzymes which create 'em—
While they in turn, with little doubt,
Depend on genes, but hate 'em.

It seems that life inside the cell
Is jealous and hierarchical:
It's very odd to find such hell
In such a *tiny* article.

Letters to the Editor

PRIVATE PATIENTS IN THE NATIONAL SCHEME

SIR,—The complex arguments of your annotation and the ensuing letters have blurred the simple issue: free drugs were promised to all, irrespective of whether they were private or N.H.S. patients. Under existing arrangements, the private patient is in danger of receiving the lower grade of treatment which you so rightly deplore, since in treating his private patient the doctor is tempted to be unwisely economical in the use of drugs that are many times the cost of the consultation fee. This inevitably invites the conscientious G.P. to encourage his private patient to join the uniformed ranks of N.H.S. patients.

Your comments seem to imply that this would be a desirable policy. Yet one of the greatest dangers of our times is the pressure that is constantly thrust upon us to conform to the standards of the multitudes. Let the discriminating be encouraged to spend their money as they please, and let this choice be extended into the realm of professional services. By these means, those that dread food-office waiting-rooms, dreary delays, and hurried consultations, can enjoy the trimmings which a free society should offer.

Department of Surgery,
Queen Elizabeth Hospital,
Edgbaston, Birmingham.

N. E. WINSTONE.

SIR,—As an intelligent and humane person I find myself inevitably in complete agreement with your opposition to boxing, and I was therefore glad to see the letter from Dr. Waycott in last week's *Lancet*. My attention was arrested by the truth of his final paragraph, and I could not resist the temptation to transfer it in context to another matter that is currently exercising the minds though not the intelligence of many of your correspondents—namely, the very real threat of two standards of treatment in the N.H.S., to which your recent annotation alluded with complete clarity and justice.

It is not entirely Abraham Lincoln's responsibility that the West is dedicated to the proposition that all men are created equal in the sight of God. This is said to be a Christian country and therefore, in principle at least, Lincoln's dictum was accepted some little time before Gettysburg—in fact shortly after the landing of St. Augustine. This, in Dr. Waycott's words, is the underlying principle that some people find difficulty in grasping. Under it, a doctor cannot escape the conclusion that no man's body is more important than another's. If he does adopt two standards of practice, and gives an inferior service to those who cannot or will not pay the money demanded, he has not only ceased to be a Christian but is no longer civilised, since he has abandoned the Christian ethic on which Western civilisation, whether we like it or not, is founded. Thus it is no defence for a man to offer the excuse that he never was a Christian anyway.

The more intelligent of your readers will perceive that private practice is not open to condemnation when it is the only form of practice available, as for example in the U.S.A. A State service is not compulsory. But if a State service is accepted—and the medical profession of this country *has* accepted it—then the mandate for private practice disappears immediately and completely. How can it be otherwise? If a doctor renders two standards of care he is sinning against God. If he does not, he is a cheat, because he is charging his patients money for something to which they are entitled free of cost.

One other point, if you will bear with me. Dr. Howard, also in last week's issue, attempts to uphold the fee-for-service system by quoting certain examples of it, such as obstetrical work and domiciliary consultations. But why should such services be so remunerated? Why should they not be part of the job for which the man is paid a fair salary? I have the temerity to suggest that if domiciliary consultations carried no extra pay they would very soon be reduced in number to those that are really necessary, and that that number would be found to be a small fraction of the present inflated figure. Is a domiciliary visit really necessary for tonsillitis?

Swansea. M. E. N. SMITH.

BRETYLIUM TOSYLATE IN THE TREATMENT OF HYPERTENSION

SIR,—Recent reports and observations in your journal [1 2] on the use of bretylium tosylate prompt us to record our preliminary impressions of the use of adrenergic-blockers in the management of patients with severe hypertension.

We have so far treated 26 patients with bretylium tosylate and 8 with the longer-acting guanethidine drug, 'Ismelin'. In our series no patient has had an initial diastolic blood-pressure of below 120 mm. Hg, and in fact, three-quarters of them have had pressures of 140 mm. Hg or higher. A large proportion of them had previously been treated with ganglion-blocking agents.

Using bretylium tosylate, the difficulties with tolerance and instability that we have encountered are essentially the same as those recorded by Dr. Turner and Dr. Lowther. In view of our experience with three patients who responded dramatically to subcutaneous bretylium tosylate, we are exploring the responsiveness to parenteral treatment of those patients who have become tolerant to oral therapy.

Of the side-effects, nasal stuffiness seems to be the most common but least troublesome. We have not seen dizziness in the absence of postural hypotension, but unexplained exertional dyspnœa has been so prominent in some cases as to limit the dose administered. We have encountered severe parotid pain, but excessive salivation and sweating have not been seen, and no patients have complained of tinnitus. Diarrhœa is readily controlled with propantheline bromide.

It seems to us that the two most serious side-effects are mental changes and profound muscular weakness. In 1 patient who was on a high dose of bretylium tosylate a confusional state with hallucinations developed but abated on withdrawal of the drug. Another patient on ismelin developed a paranoid psychosis which recovered on cessation of treatment, and recurred when the drug was restarted. Profound muscular weakness with abnormal electromyographic patterns necessitated the withdrawal of bretylium tosylate in another patient.

The introduction of adrenergic-blocking drugs is clearly a major advance in the treatment of severe hypertension. The large majority of patients previously treated with ganglion-blocking drugs prefer bretylium tosylate because of the relative absence of side-effects. Tolerance has however been more frequent and troublesome with bretylium tosylate than with the ganglion blockers and this has demanded much closer supervision of patients in the follow-up clinic. Apart from this problem of increasing tolerance, bretylium tosylate suffers from the disadvantages common to all the relatively short-acting antihypertensive drugs. Our experience with the longer-acting ismelin has shown it to be a promising advance, though it is, as yet, too early to comment on its long-term usefulness.

We endorse the view that at this early stage in the use of these new drugs, anyone using them should be fully aware of their disadvantages, and particularly of the possibility of their causing toxic psychoses or profound muscular weakness.

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JOHN M. EVANSON
H. T. N. SEARS.

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POTASSIUM PERCHLORATE IN THE TREATMENT OF THYROTOXICOSIS

SIR,—In their interesting article of Feb. 20, Dr. Crooks and Professor Wayne advance the claims of potassium perchlorate as the drug of choice in the treatment of thyrotoxicosis. During the past 18 months we have prescribed potassium perchlorate with increasing frequency, and experience of 70 cases supports their opinion that this preparation is both effective and relatively free from toxic effects.

Crooks and Wayne report its use as a preoperative agent and cite 20 operation cases in which there was no technical difficulty due to increased vascularity, despite the fact that preliminary iodine was advisedly omitted in order to avoid the danger of an acute exacerbation of thyrotoxicosis. Nevertheless, it should be noted that 18 of these patients had small nodular goitres, and it would be wrong to assume that operation for the diffusely enlarged gland of primary thyrotoxicosis will prove equally trouble-free. Certainly in the series of 13 operation cases reported by Godley and Stanbury [1] hæmostasis presented a difficult problem in 1 patient, and in 2 others severe tachycardia imposed hemithyroidectomy in place of the proposed subtotal thyroidectomy.

Up to date no substantial series of operation cases prepared with potassium perchlorate has been published, and opinions based on a few cases are apt to be misleading. However, it is important for the surgeon to know what to expect at operation: is increased vascularity likely to prove hazardous, and does potassium perchlorate provide adequate control of the thyrotoxicosis both during and after operation?

After preparation with potassium perchlorate, but omitting iodine, we have operated on 24 patients with primary thyrotoxicosis and 3 with toxic adenoma. Routine subtotal thyroidectomy with exposure of the recurrent laryngeal nerves was carried out in all cases. In 1 male patient with a large diffuse goitre control of bleeding was exceptionally difficult and transfusion was required. In addition more than average vascularity was a feature in 7 diffusely enlarged glands, although no anxiety was caused on this account. In 1 patient severe tachycardia persisted during operation and for the following three days; but, in retrospect, this patient may have been submitted to operation whilst still toxic. With this possible exception control of the thyrotoxicosis was fully maintained during and after operation. The remaining operations were uneventful. In several patients the thyroid gland was surprisingly pliable and unusually easy to manipulate and this may well have been related to the omission of iodine in preparation for operation.

It appears, therefore, that the surgeon who uses potassium perchlorate must be prepared to meet some difficulty from hæmorrhage. Our policy at present, with the possibility of eventual surgery in mind, is to treat the primary thyrotoxic patient with a large vascular gland with carbimazole ('Neomercazole') so that in the event of operation iodine may be used to reduce vascularity. For the remainder we tend to prescribe potassium perchlorate, which appears to be as effective as other antithyroid drugs and perhaps less toxic.

Thyroid Clinic,
David Lewis Northern Hospital,
Liverpool.

W. H. R. COOK
PHILIP HAWE.

SIR,—With interest I read that Dr. Crooks and Professor Wayne recommend potassium perchlorate as the antithyroid drug of choice because of its relative high effectiveness and its low toxicity. The question of recurrence was not discussed.

In a group of 23 patients suffering from thyrotoxicosis who were treated with potassium perchlorate, immediately satisfactory results were obtained in 21, while in 2 patients operation proved necessary.[1] Transient loss of hair was the only side-effect observed. Questionnaires were sent to the patients on an average thirty-one months after the conclusion of the treatment, and contact was established with 20 out of 21. 12 of the patients stated that they enjoyed good health. Recurrence had taken place in 8 patients. It seems that the high rate of recurrence limits the indications for potassium perchlorate in thyrotoxicosis.

Frederiksberg Hospital,
Medical Department E,
Copenhagen.

JOHANNES MOSBECH.

1. Godley, A. F., Stanbury, J. B. *J. clin. Endocrin.* 1954, **14**, 70.

MEDICAL NEEDS OF INDIA

SIR,—In your leader of Jan. 30 appears the blunt statement that "the Government (of India) does not look with favour on missionary effort". It is qualified by a passing appreciation of the Vellore Christian Medical College, but nevertheless gives an unfortunate and misleading impression.

This, the greatest international and interdenominational venture of the Christian Church in the world today, is no proselytising machine, but a united demonstration of the Christian Gospel and its social implications, in cooperation with the United Church of South India. Of course there are, as one might expect, voices raised in criticism and opposition by the devotees of other religions and by ardent nationalists. But these must be balanced by the opinions and statements of Indian leaders, and of these we have many, the latest coming from Mr. Nehru himself. He writes from Delhi Feb. 5, 1960: "I am glad to learn that Miss Eileen Joyce is coming to India and giving a series of concerts in aid of the Vellore Medical College and Hospital. I think this hospital has done excellent work and deserves every help and encouragement." Mr. Nehru was hoping to attend the concert to be given in Delhi in company with his friend the late Countess Mountbatten, one who has been outstanding in giving that "help and encouragement" to Vellore.

London, W.1.

CLEMENT C. CHESTERMAN
Chairman, Friends of Vellore.

AUTOGENOUS VACCINES AND THE COMMON COLD

SIR,—The report in your issue of Feb. 13 is interesting and important, as are the criticisms by Dr. Ritchie last week.

With his criticisms I entirely agree, but I should like to add the further comment that basically this report is a repeat of Dr. Ritchie's original contribution.[2] A repeat—therefore a check or control—on another worker's claims, especially if these break any new ground, is always of value, provided it conforms to certain simple but essential rules. But this trial has breached the first rule of such re-tests—namely, that they must carry out exactly the original conditions.

The least valid of the three main reasons given for this variation is: "Furthermore there seemed to be no theoretical reason why weekly injections should produce a better immunological response than a more usual course." This opinion is quite unsupported by argument.

In consequence the value and importance of Dr. Ritchie's results remain untouched.

To check or diminish the incidence of the common cold part-two—i.e., the non-virus stage—would be a major service to the community. The Common Cold Centre has recently called for volunteers to enable them to push on with this invaluable work. Here is a real opportunity for a proper trial of Dr. Ritchie's methods, with other controls using stock proprietary vaccines, observing the full directions for each method. If the results are favourable towards Dr. Ritchie's method, as

1. Mosbech, J. *Ugeskr. Laeg.* 1959, **121**, 1166.
2. *Lancet*, 1958, i, 615.

my very small packet of cases suggest, the difficulty of weekly administration should be no more than that of training diabetics to give themselves insulin. And what sufferer from frequent colds would not give himself a hundred injections if there was any chance of avoiding these repeated miseries?

Chipping Campden, Gloucestershire. C. B. HEALD.

CIRCULATION IN LOWER LIMB BEFORE AND AFTER RECONSTRUCTION OF OBSTRUCTED MAIN ARTERY

SIR,—We read the paper of Dr. Snell and his colleagues (Jan. 30) with particular interest, since we undertook a similar but less extensive investigation with H. T. John* while students of Prof. R. S. Pilcher at University College Hospital, in 1955–57. Since our findings confirm some of those of your contributors, we submit a brief account of our experiments.

We studied the blood-flow to the whole of the leg below the level of the superior border of the patella. This was in order to include as much as possible of the territory of the femoral artery below its commonest site of obstruction at the adductor-magnus opening. It was intended to investigate flows in the calf and foot separately at a later stage.

Measurements were made with the subject lying flat and the leg enclosed in a water-filled plethysmograph at 35°C±0·5°C. In a normal limb 2 minutes' occlusion of arterial inflow was found to produce a significant rise in flow measured 7·5 seconds after dropping from occluding to collecting pressure (this delay was introduced to avoid cuff artefact), whilst the resting flow measured 3 minutes later was not significantly changed.

In order to estimate the resting flow (R.F.) and the post-occlusion flow (P.O.F.) of a limb we made 10 measurements at 3-minute intervals over a period of 30 minutes; 5 of the determinations (chosen at random) were preceded by 2 minutes' arterial occlusion. Mean values of R.F. and P.O.F. for the session were calculated from these results. As a similar limb segment was used on each occasion and no significant relationship was found between flow and the volume of the segment in which it was measured, results are expressed in ml. per min.

We investigated groups of patients with normal and claudicating limbs, which were not matched in any way. In each limb R.F. and P.O.F. were estimated under standard conditions. In one limb the claudication was due to a thrombosed popliteal aneurysm and was successfully treated surgically.

In fig. 1 the estimate of P.O.F. is plotted against the estimate of R.F., for normal and claudicating limbs.

* Formerly surgical registrar, University College Hospital, now at Peter Bent Brigham Hospital, Boston, Mass.

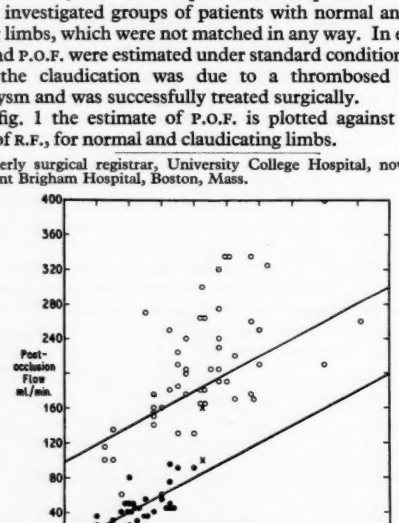


Fig. 1—Relation between resting flow and post-occlusion flow estimations in limbs with (●) and without (○) claudication. The pre- and post-operative situations in grafted subject are included (x). P.O.F. = R.F. +100, and P.O.F. = R.F. are drawn for comparison with normal and diseased groups respectively.

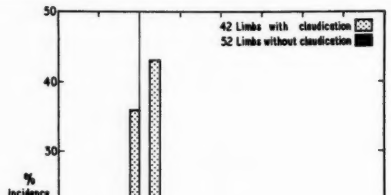


Fig. 2—Incidence of given values of the difference (P.O.F. — R.F.) between post-occlusion and resting-flow estimations in normal and diseased groups. (Difference grouped in intervals of 20 ml. per min.)

Regression equations for the two groups have been calculated as follows:

Normal limbs: $y = 1{\cdot}2x + 106{\cdot}0$ ($P = 0{\cdot}001$)
Claudicating limbs: $y = 0{\cdot}9x + 0{\cdot}7$ ($P = 0{\cdot}001$)

These results suggest that the effect of 2 minutes' arterial occlusion in normal limbs is to raise the flow to the segment by about 100 ml. per min. irrespective of limb size or the value of the resting flow, and that this response is absent in the claudicating limb. In the limb which was surgically treated the response was restored (fig. 1).

Using the difference (P.O.F.)–(R.F.) in a limb as a measure of the magnitude of the hyperæmic response a clear distinction between normal and claudicating limbs can be made (fig. 2).

Our results support the finding of Snell, Eastcott, and Hamilton that there is an altered response to a period of arterial occlusion in a limb with main-vessel obstruction, and that this can be restored by surgical relief of the obstruction.

We report our findings because we have been able to demonstrate this phenomenon using a period of occlusion of arterial inflow which leaves the resting flow unchanged 3 minutes later, and makes possible repeated observations of the response on one occasion. Consequently, the usefulness of the response as an investigatory tool is increased.

R.A.F. Institute of Aviation Medicine, Farnborough, Hants. J. L. GEDYE
University College Hospital, London, W.C.1. D. J. RILEY.

HYPOGLYCÆMIA ASSOCIATED WITH SARCOMA

SIR,—In your issue of Jan. 23, Dr. Macnaughton and Dr. Priest describe a case of hypoglycæmia associated with a sarcoma, and discuss four hypotheses accounting for the hypoglycæmia. I should like to present a fifth hypothesis and suggest a test for its verification.

A tissue analysis by Sellman et al.[1] of a sarcoma associated with hypoglycæmia revealed a tenfold increase of almost all aminoacids over the levels in control tissues. Furthermore, Cochrane et al.[2] described several cases of hypoglycæmia following the administration of protein, leucine, or isovaleric acid. Therefore, a plausible hypothesis is that some or all large sarcomas send an excess of aminoacids into the blood, and when this occurs in a leucine-sensitive individual, hypoglycæmia results. Since leucine and casein test-meals have no effect on the blood-sugar levels of normal individuals it would be interesting if Dr. Macnaughton and Dr. Priest would do

1. Sellman, J. C., Perkoff, G. T., Null, F. C., Kimmell, J. R., Tyler, F. H. *New Engl. J. Med.* 1959, **260**, 17.
2. Cochrane, W. A., Payne, W. W., Simpkiss, M. J., Woolf, L. I. *J. clin. Invest.* 1956, **35**, 4.

this test on their patient if she is alive and has symptoms. If the test-meal produces hypoglycæmia then this is the probable mechanism of her hypoglycæmia when the tumour was present.

Mount Sinai Hospital, New York. JERE B. STERN.

HÆMORRHOIDS

SIR,—Your leader of Feb. 20 on hæmorrhoids makes a lot of ado about little. Bleeding internal piles, if unprolapsed and uncomplicated, are easy to diagnose and easy to treat.

The history of splashing bright blood on the sides of the closet on defæcation is diagnostic. The equipment necessary to see piles is of the simplest possible—a tubular metal speculum 3–4 in. long, 1 in. in diameter (a smaller size is necessary in case of tight anus), and an electric light adjustable on a floor pillar. The speculum is pushed in until the mucosa of the anterior rectal wall is seen and then withdrawn until first the anorectal ring and then the anal canal, with its piles, are seen. The piles, unsupported by the opposite anal wall, bulge into the lumen over the end of the speculum, and can easily be injected. If they have been bleeding recently they will often bleed now before being pricked. 20% phenol in glycerin has proved safe and certain in 25 years' practice. No more than 1, 2, or 3 drops should be injected into each pile, according to size. A narrow 2 ml. syringe and a fine needle 2 or 3 in. long are necessary. Under no circumstances should 5% phenol in almond oil be injected in quantity above the piles; it is very painful and has led to infection and other complications.

The method I describe is quite painless unless the needle is put in close to the edge of the anus. As for position, the old left lateral position, bottom to the edge of the couch, head over to the far side, knees drawn up, enables one to diagnose and treat without an assistant.

I have always treated hospital patients with piles in the general run of outpatients and never sent them to a clinic.

Proctitis can be diagnosed through the same speculum as used for piles. Digital examination of the rectum with counter pressure on the lower abdomen is always done before using the speculum and this is usually enough to exclude carcinoma of the rectum. Of course, one has to know about fissure, fistula, papilloma, and other possible conditions and take account of them in the history-taking and preliminary examination, but by and large piles are one of God's gifts to the surgeon; he can quickly, safely, and certainly bring relief to his patient.

You are right in emphasising the need for a second or third look at intervals of a few weeks.

Edgbaston, Birmingham. FAUSET WELSH.

SIR,—In your leading article you state that the sufferers "become the worst of patients—truculent in seeking advice, erratic in following it, always willing to take their own discharge once in hospital." This suggests that they belong to a recognisable group as regards their character formation. In fact these traits are typical of fixation in the anal stage of development, the normal manifestation of which is a period of obstinacy and negativism in the second year of life (Freud 1908, Abraham 1921, 1924).

Other writers—for example, Felix Deutsch—have pointed to the link between the zone of fixation and the subsequent development of organic symptoms in that zone. According to such theories the relationship between truculence in the personality and symptoms in the anal region would not be one of chance.

You mention as an ætiological factor "bad bowel habits inculcated in childhood" and state that tracing them back "is hardly practicable". This misses the point that such bowel habits are seldom simply the result of faulty education, but are maintained because they provide unconscious erotic pleasure. The remarkable exacerbations and remissions of hæmorrhoids can often be related to fantasies affecting the anorectal zone and giving rise to anxiety, such as unconscious desires for anal intercourse, or fantasies of giving birth, as in *couvade*. This is not to say, of course, that all hæmorrhoids are caused by unconscious fantasies, or that they are caused by unconscious fantasies only, or that treatment along physical lines may not at a certain stage be the only method of dealing with them.

You describe patients who never see the surgeon because he examines them only from the rear. It is also true that these surgeons never see the patient, only the patient's rectum. They are therefore unlikely to become adept at detecting the emotional conflicts behind the localised symptoms. When doctors are more extensively trained in the recognition and evaluation of emotional abnormalities, both treatment and the patients' relationship with the doctor are likely to be more satisfactory.

London, W.1. JOHN KLAUBER.

THE ROYAL COMMISSION

SIR,—Truth has many facets, and who shall say from which angle the truest view can be obtained? In your issue of Feb. 27 Dr. Roe writes "The B.M.A. has for the first time departed from its usual practice of serving only the vested interests of the part-time consultants." This is a delightfully novel point of view to me.

Every year I consider joining my colleagues who have resigned from the B.M.A. because of its relative indifference to the cause of consultants, but every year I seem to forget to cancel my banker's order in time. The same oxlike patience kept us waiting humbly for the crumbs which never fell from Danckwerts' table, at which I seem to remember that the general practitioners had a pretty fair tuck-in. Had the B.M.A. nothing to do with that?

Plymouth. MICHAEL REILLY.

THE ABNORMAL APPENDIX

SIR,—In answer to Mr. Bolam's letter (Feb. 13) may I make the following observations?

The case for the paramedian or gridiron incision has been adequately discussed in the past, particularly in correspondence in *The Lancet*, in 1953, and there will always be controversy on this subject.

I should not like to be considered guilty of using a paramedian incision in order to carry out an exploratory laparotomy without attempting to make a specific diagnosis before operation. It is my custom to get newly qualified housemen to make a specific diagnosis before the abdomen is opened, and furthermore should the diagnosis be one of appendicitis, to state where they expect the appendix to be lying and what it will look like. In this way we can hope to be honest about the diagnosis and if we are right in our findings congratulate ourselves, or if wrong learn from our mistakes. In adopting such a policy I have found how often one can err in assessing just what the organ will look like and where we can expect to find it. My incision is, of course, placed according to where I expect the appendix to be found.

I also like to think that one does not open the abdomen willy-nilly for abdominal pain, and that the proportion of normal appendices removed is a reasonable one. I agree with Mr. Bolam that quite a large number of patients are admitted to hospital with a diagnosis of possible appendicits, and that in a proportion of cases no diagnosis can be made initially, and in some no diagnosis can be made at all, but certainly the abdomen should never be opened without adequate care and forethought.

It is my custom, particularly in the case of a child, to examine the abdomen again and again until one is perfectly happy that no harm will come as a result of conservative treatment, or, conversely, decide that operation is indicated for a very good reason. One sees cases which have been treated conservatively elsewhere, but which develop a second attack of appendicitis, and it is my impression that these cases are more likely to

develop the obstructive type of appendicitis on the second occasion.

The gridirons which develop in incisional hernia are, I believe, a major undertaking particularly when strangulated gut is contained in the sac.

Weymouth and District Hospital, Weymouth. JOHN M. E. JEWERS.

SEVERE HYPERSENSITIVITY TO SULPHAMETHOXYPYRIDAZINE

SIR,—I read with considerable interest the article (Jan. 23) on this condition, since I recently had two similar cases in my general practice.

The first was a 21-year-old coloured female who was being treated for a tubo-ovarian abscess, and the second a 10-year-old white female who had pyelitis for which the drug was being given. The course of the hypersensitivity reaction was almost exactly the same as described by Dr. Maher-Loughnan and Dr. Tullis, except that the eyes were apparently much more severely affected in my cases. In fact, we feared that the coloured patient would lose her vision. Both patients recovered completely on dexamethasone, the child much more promptly than the adult.

Interestingly enough, at a recent conference on rheumatic fever, I heard the group from Duke University Medical School mention that they had discontinued using "long-acting sulphonamide preparations" for prophylaxis of rheumatic fever since they seemed to be having an increased incidence of Stevens-Johnson syndrome with the use of these preparations.

Possibly these very serious reactions are more common than reports indicate. I have almost stopped using them.

York, South Carolina. G. F. HIOTT, Jr.

CORTICOSTEROID PURPURA

SIR,—Professor Scarborough and Dr. Shuster's preliminary communication on this subject (Jan. 9) confirms the observation reported by Scott, Hudson, Goodman, and myself in 1953 [1] that in some subjects treated with corticosteroids the discoloration due to spontaneously occurring or experimentally induced bruises often persists for an unusually long time. Our study included two subjects treated with corticotrophin.

Professor Scarborough and Dr. Shuster presume that the delay in resorption of extravasated or injected blood is due to inhibition of an inflammatory response by corticosteroid and they imply that it is the cellular response which is at fault. When we first noticed delayed bruised dispersion we too suspected that this was the explanation, for Gell and Hinde [2] had shown impairment of macrophage response in inflammatory reactions in rabbits treated with cortisone and corticotrophin. However we had difficulty in accepting this conclusion because, in the intradermal lesions which we excised in untreated subjects, phagocytosis was so inconspicuous that we doubted if an impaired macrophage response alone could account for the delay. Our doubts were strengthened by the more detailed histological studies which we described of bruise dispersion in guineapig skin.

A striking feature in these lesions was the number of erythrocytes which lie free between the collagen bundles, and it seemed possible that corticosteroids might modify the normal process of dispersion of erythrocytes away from the lesions through the network of collagen. However we reached no definite conclusion on the mechanisms involved. The process of removal of intradermal erythrocytes is certainly complex and it will be interesting if Professor Scarborough and Dr. Shuster's extended studies throw further light on this problem.

The Royal Melbourne Hospital, Parkville, Victoria. RICHARD LOVELL.

1. Lovell, R. R. H., Scott, G. B. D., Hudson, B., Osborne, J. A. *Brit. J. exp. Path.* 1953, **34**, 535.
2. Gell, P. G. H., Hinde, I. T. *ibid.* 1951, **32**, 516.

KALURETIC EFFECT OF HEPARIN

SIR,—In view of the observations of Dr. Schlatmann and his colleagues and of Dr. Cejka and his coworkers in your issue of Feb. 6, concerning the natriuretic effect of heparin in human subjects, it seems of interest to record observations made during acute experiments on trained unanæsthetised dogs in the department of surgery, Peter Bent Brigham Hospital, Boston.

Before each experiment the animal was fasted for 24 hours, but allowed water ad lib. It then lay quietly on its side during a 3–4 hour experimental period. A control experiment of similar duration was conducted in each animal some days before the definitive experiment. Urine was collected at 15-minute intervals from an indwelling bladder catheter, the bladder being washed twice with 10 ml. distilled water at the end of each collection period. After 2–4 preliminary collection periods, during which the electrolyte excretion-rate was similar to that found throughout the control experiment, sodium heparin (30–50 mg. in 0·3-1·0 ml.) was injected intravascularly. Urine collections were continued for 1–2 hours subsequently. The results of one representative experiment are given in table I. In two of the experiments in this animal, the heparin was injected via a permanent indwelling polyvinyl catheter in the common carotid artery, but intravenous injection on one occasion produced a similar effect.

TABLE I—EFFECT OF HEPARIN ON POTASSIUM AND SODIUM EXCRETION IN NORMAL DOG

Dec. 8, 1959

Collection period (15 min.)	K excretion (μEq. per min.)	Na excretion (μEq. per min.)
1	10	9
2	6	5
3	5	6
4	4	6
50 mg. heparin sodium intravenously at start of period 5		
5	7	6
6	23	7
7	30	5
8	35	6
9	34	7

In each animal a three- or four-fold increase in potassium excretion appeared within 30 minutes of heparin administration. This increase persisted for the ensuing 1–2 hours of the experiment, but tended to decline towards the end. The experiments have not been continued beyond this time. Sodium excretion did not change appreciably during the period studied.

This pattern of change in electrolyte excretion differs from that described by Schlatmann et al. in that (*a*) the effect was immediate and (*b*) the affected ion was potassium. Schlatmann et al. found no change in electrolyte excretion during the first 36 hours after beginning heparin therapy, and thereafter a sodium diuresis with possible potassium retention was noted.

Cejka et al. relate the late sodium diuresis in their human subjects to the concomitant decrease in urinary aldosterone. It is obvious that the kaluresis noted in the dog could not be attributed to a diminution in aldosterone secretion, since this would be expected to result in an unchanged or possibly diminished potassium excretion. The alternative possibility of an actual increase in aldosterone production appeared unlikely in view of the very rapid onset of increased potassium excretion (i.e., within 30 minutes), but an experiment on an adrenalec-

TABLE II—EFFECT OF HEPARIN ON POTASSIUM AND SODIUM EXCRETION IN ADRENALECTOMISED DOG

Serum Na = 146 mEq. per litre, serum K = 4·5 mEq. per litre

Collection period (15 min.)	K excretion (μEq. per min.)	Na excretion (μEq. per min.)
1	4	16
2	5	16
3	4	13
4	5	13
30 mg. heparin sodium intracarotid at midpoint of period 5		
5	5	13
6	11	9
7	17	8
8	18	12
9	18	12

tomised dog is of direct interest in this respect. The animal had been maintained for some weeks after operation with 25 mg. cortisone acetate and 0·2 mg. 9-α-fluorohydrocortisone daily by mouth, and was clinically apparently normal, with normal serum-electrolyte levels. An experiment carried out 24 hours after the last dose of replacement therapy is summarised in table II. 30 mg. of heparin given intravascularly was followed by a kaluresis similar in timing and magnitude to that seen in the dog with intact adrenals. It is clear therefore that the immediate kaluretic effect of heparin cannot be ascribed to an alteration in aldosterone secretion.

These observations are, of course, restricted to the hour or two immediately following heparin administration. The observed effect on potassium excretion, though clearly visible under these experimental conditions, is nevertheless a small one in absolute terms, and might conceivably be overlooked in a metabolic balance study in human subjects without the obvious advantages of short-term catheter collections of urine. The data are offered in the light of this realisation, and in order to complement the important studies of Majoor and his colleagues on the mechanism of heparin-induced diuresis.

Department of Medicine, University of Manchester. FRANCIS P. MULDOWNEY.

Columbia University College of Physicians and Surgeons, New York. PETER BANKS.

ORAL CONTRACEPTIVES

SIR,—In her letter last week Dr. Mears states that experts are agreed that the oral administration of hormonal substances as contraceptives is harmless and the substances are not carcinogenic. I do not know whether I would be accounted an expert, but I take leave to disagree.

One-sixth of women with a granulosa-cell tumour of the ovary develop carcinoma of the corpus uteri.

A patient who developed amenorrhœa due to her incarceration in a concentration camp during the war was given œstrogen/progesterone therapy on her release so as to restore menstruation. She continued on this therapy for seven years and then came to me with malignant disease of the uterus.

A patient with a benign arrhenoblastoma of the ovary with defeminisation over two years recovered on removal of the tumour and promptly fell pregnant. The child weighed only 3 lb. 15 oz. at term. Since then, though still in the early thirties, the woman has had intermingled amenorrhœa and such metrorrhagia as to need blood-transfusion. So convinced was I that the growth must have recurred that I reopened her abdomen but found nothing abnormal. I can only conclude that the prolonged production of male hormone had produced permanent effects on the other endocrine glands, possibly the pituitary.

It could be argued that the amounts and nature of the hormones in these examples are not the same as those which it is proposed to use in the trial, but nevertheless if sufficient amounts of any substance are given to suppress ovulation over a long period it is likely that in some of the victims permanent effects will be produced and in others undesirable changes will occur.

Newcastle upon Tyne. FRANK STABLER.

SIR,—Dr. Eleanor Mears states that our product 'Secrosteron' is among three progestationally active substances undergoing trial as an oral contraceptive. Although secrosteron is unique among presently available progestationally active steroids in its apparent freedom from concomitant androgenic properties, our own studies in animals have failed to reveal any ovulation inhibitory action at the equivalent of normal therapeutic dosage. We would no longer regard secrosteron as being worthy of trials as an oral contraceptive.

We have, however, discovered in further research hitherto unknown steroids which in animals are considerably more active progestationally (up to 200 times more) than secrosteron and highly active also as ovulation inhibitors. Moreover they are apparently free from the side-effects associated with other steroids that have so far been used. The possibility of such enhancement of activity, by requiring smaller daily dosage, seems likely sufficiently to diminish the daily cost as to bring them within the realm of consideration for use, particularly for underdeveloped countries with rapidly expanding populations—a necessary feature, as Dr. Mears so rightly stresses. We hope to publish further details of the products being studied as soon as possible.

FRANK HARTLEY
Scientific Services Director,
The British Drug Houses Ltd.
London, N.1.

EFFECT OF PROLONGED CAGING OF DOGS

SIR,—Friends in the United States have asked us to obtain, as a matter of urgency and for submission to a Congressional Committee, authentic information as to the technical effects on laboratory dogs of close and prolonged caging.

The Food and Drug Administration is carrying out long-term toxicity tests of aniline and other colourings used in human food, and for this purpose beagles are housed, from the age of 3 months, in cages measuring approximately 30 in. by 36 in., in which they remain for $2^1/_2$ to 3 years, the cages being washed down without removal of the dogs. It is claimed that the provision of exercise runs, even if these were uniform in construction and use, would impair the validity of the tests. The results of these will be applied to human beings living under normal conditions.

We should be most grateful if any of your readers could supply us with any information bearing on the methodological aspect of prolonged and close caging.

C. W. HUME
Universities Federation for Animal Welfare.
7a, Lamb's Conduit Passage, London, W.C.1.

LOBECTOMY FOR BRONCHIAL CARCINOMA

SIR,—I find it hard to understand why Mr. Belcher's analysis [1] omitted the operative mortality and the patients lost to follow-up, and why patients who died during the first five years from other causes were included as five-year survivals of the disease. Any analysis on a study such as this seems totally unreliable. There are certain basic fundamental rules of statistical analysis which certainly preclude the type of analysis reported in this paper.

Ochsner Clinic, New Orleans. PAUL T. DECAMP.

*** We showed Dr. DeCamp's letter to Mr. Belcher whose reply follows.—ED. L.

SIR,—The operative mortality in the series was clearly given as 12 (4·5%). This was excluded from the analysis to bring the paper into line with many other publications on bronchial carcinoma.

The number of patients lost to follow-up was clearly stated as 6 (2%), and again it was made clear that these had been excluded from the total number of patients to be analysed. Even had they all died the total survival-rate would not have been greatly altered.

I am at a loss to see how Dr. DeCamp has interpreted the figures in such a way as to suggest that I have included the "deaths from other causes" as "survivors". The 30 patients concerned were excluded from the number considered to be "at risk" in part of fig. 1, but were included in all the other figures.

1. *Lancet*, 1959, ii, 639.

The paper was written for clinicians who fortunately do not always feel themselves bound to abide by the rigid and often arbitrary rules laid down by some statisticians, and to say that the figures are " totally unreliable " seems to me to be totally unjustifiable.

The London Chest Hospital, London, E.2. J. R. BELCHER.

PRECORDIAL CATCH

SIR,—I have read with interest the various letters on this subject. These pains are well known and are described by Sir William Broadbent in his textbook and by many of the older authors. At St. Bartholomew's Hospital they were described by the patients as " pangs around the heart ". Dr. Geoffrey Evans simply called them " heart pang ", and as this they are known by Barts men, and probably many others.

General Hospital, Singapore. G. A. RANSOME.

ANTI-SMOKING CAMPAIGN

SIR,—Although the Edinburgh campaign was largely a failure, a " postmortem " on the probable causes of failure could be of value to planners of future anti-smoking campaigns, and I congratulate Dr. Thomson and his team (Feb. 6) on pioneering the first properly organised anti-smoking campaign in this country. I have been campaigning against smoking on my own account and on behalf of the National Society of Non-Smokers (on an almost non-existent budget!) for over 30 years, and I likewise have experienced much failure, but also some success. I should like to comment.

The campaign material seems to have been well presented—as well as the absence of television and radio would allow. But from perusal of the descriptive article and some of the material, I think it probable that a major cause of failure was that the material used was insufficiently damaging to smoking. The campaigners appear to have fought with one hand behind their back. The most fundamental, important, and damning fact about smoking is its nature, and this does not seem to have been mentioned. Though smokers are usually extremely loth to concede this—because the implications spell doom to smoking—smoking tobacco is on all fours with smoking opium or hashish.[1] It is a drug addiction, a disease. All tobacco smokers suffer, in varying degree, from chronic nicotine poisoning, and poisoning and irritation of the respiratory tract by many other combustion products of tobacco, and such a complex poisoning is clearly no less a disease than, say, lead-poisoning.

Recognition of smoking as a disease carries colossal implications:

(1) Its cure and prevention are primarily *our* responsibility.

(2) The drug addictions are psychopathic diseases. They " border on a line between psychosis and psychoneurosis " [2] and appropriate treatment is therefore psychotherapy.

(3) Smoking is a communicable disease, and is now pandemic—to *our* shame—because

(4) it is readily preventable: it is no more difficult to prevent than opium smoking (which we now prevent).

There are many other implications [3] but these are outside the scope of a letter.

The campaign's main platform was clearly the relationship between smoking and lung cancer. But the authors are obviously not fully convinced that smoking causes lung cancer, since they refer to " the *postulated* connection " and " the *possible* association " between smoking and lung cancer (italics mine), also to " the theory " and " the hypothesis " (that smoking causes lung cancer). Any lack of conviction on this vital point would inevitably detract from their effectiveness as propagandists. The authors' and indeed the majority of people's lack of conviction about whether or not smoking causes lung cancer may well have resulted from the difficulty of understanding precisely what the Medical Research Council meant in their important statement on Smoking and Cancer of the Lung (1957).

Conclusion (4) reads: " Evidence from many investigations in different countries indicates that a major part of the increase (in the death-rate from lung cancer over the past 25 years) is associated with tobacco smoking, particularly in the form of cigarettes. In the opinion of the Council, the most reasonable interpretation of this evidence is that the relationship is one of direct cause and effect." Presumably " the most reasonable interpretation ", in the opinion of the M.R.C., is the interpretation the M.R.C. in fact puts on the evidence, and if it is further assumed that the M.R.C. accepts the evidence as reliable, it follows that, in the opinion of the M.R.C., (1) smoking causes lung cancer directly, and (2) it causes the majority of cases. Had the M.R.C. statement stated explicitly whether or not, in the opinion of the Council, smoking causes lung cancer, and, if so, whether or not it causes the majority of cases, the M.R.C.'s main purpose in making the statement—to clear up prevailing uncertainty about this vital matter—would have been fulfilled.

Granted the difficulty of obtaining suitable literature for the campaign, but the B.M.A. booklet, Smoking—the Facts, was written by a smoker. What more convincing proof of the booklet's inadequacy could be devised than its failure to cure its author?

Wallasey, Cheshire. LENNOX JOHNSTON.

REDUCTION OF SPUTUM VISCOSITY IN CHRONIC BRONCHITIS

SIR,—Dr. Palmer's work (Jan. 9) on the effect of a water aerosol on sputum viscosity has drawn attention to the importance of hydration on the viscosity of bronchial secretion.

There seems to be a diurnal variation in sputum viscosity—that produced overnight being more viscous than that expectorated during the day.[1] Dr. Palmer's measurements were made during the afternoon and it would be interesting to know the constancy of his control observations during this period.

During surgical operations changes in hydration are partly responsible for the development of sputum retention and pulmonary complications; other things to be considered are drugs and the depth and duration of anæsthesia. Increase in sputum viscosity during operation has been measured and related to the development of postoperative pulmonary atelectasis.[2] The importance of adequate hydration during and after operation by attention to fluid and electrolyte balance helps to lessen this risk of pulmonary complications.

Middlesex Hospital Medical School, Institute of Clinical Research, London, W.1. GERALD BLANSHARD.

CONTROL OF ANTICOAGULANT THERAPY

SIR,—In their letter of Feb. 13 Dr. Walker and Dr. Matthews say that a way of reducing the cost of thrombotest may be found—e.g., by using smaller volumes of blood and reagent, though so far their own experience with small volumes was not encouraging.

I want to tell your readers that such a method has been in use in our laboratory for three months now and works satisfactorily.

It consists simply in reducing all volumes in the original thrombotest method by 1 : 5—i.e., using 0·1 ml. reagent and 0·02 ml. stabilised blood or plasma. In our experience it is not significantly harder to read the coagulation time with this reduced volume than with the original technique. In our laboratory, where these readings are performed by a number of technicians with a laboratory training of two years and upwards,

1. Johnston, L. *Lancet*, 1942, ii, 742.
2. British Encyclopædia of Medical Practice; vol. 10, p. 305. London, 1952.
3. Johnston, L. The Disease of Tobacco Smoking and its Cure. London, 1957.

1. Blanshard, G. M.D. Thesis, University of Cambridge, 1955.
2. Blanshard, G. *Dis. Chest*, 1960, **37**, 75.

there has been no difficulty in using the reduced-volume technique.

Our results with the reduced-volume and with the original technique were compared in 200 duplicate analyses before we adopted the reduced-volume technique as our routine method, and the results are to be published in *Nordisk Medicin* in Danish.

With this simple device we have solved the economy side of the transition from our former method (Larsen and Plum's method) to the thrombotest method. In our experience the thrombotest is far superior in the control of anticoagulant therapy.

Central Laboratory,
Svendborg County Hospital,
Denmark. TORBEN K. WITH.

ISCHÆMIA OF FOREARM AFTER INTRAVENOUS INJECTION

SIR,—I feel that the following case should be recorded.

On Sept. 13, 1959, a fit 30-year-old man was given anti-tetanus serum. About three-quarters of an hour later he returned with a severe reaction and was given adrenaline intramuscularly in the buttock and promethazine 50 mg. intravenously in the left antecubital fossa. At the end of the intravenous injection he experienced a transient shooting pain at the tip of the left elbow. The pain ceased at once, and as after half an hour he appeared to be all right, he was sent home.

He was completely comfortable for three hours and then had acute pain in the left forearm with "pins and needles" and severe cramps. Four hours after the onset of this pain he came back to hospital at 1.15 A.M. on Sept. 14.

The left forearm was dusky, mottled, cold, swollen, tense, and acutely painful from elbow to wrist. The hand appeared to be unaffected and warm and the radial pulse was normal.

At 3.15 A.M. left brachial-plexus and stellate-ganglion block relieved the pain, improved the colour somewhat, reduced the tension, and the arm became warm. He was also given pethidine and phenoxybenzamine (' Dibenyline ').

Pain started to return at about 8.30 A.M. A second plexus and ganglion block at 10.20 relieved the pain and slightly improved the colour but had no appreciable effect on the tension. As soon as possible Mr. E. W. Bintcliffe incised the deep fascia of both anterior and posterior muscle compartments to relieve the tension. Healthy-looking muscle under considerable tension bulged through the incisions and œdema fluid oozed out. Subsequently the hand and upper arm became swollen but it was possible to suture the incisions in stages, seven to fourteen days later. Two superficial areas of skin necrosed but have now healed, and the muscle function has almost completely returned and is still improving.

Appearance of forearms on Oct. 27.

The ulnar artery in the right arm was abnormal, arising high and running superficially in the forearm, and it seemed that the common interosseous artery in the left arm must have been in spasm. It was unlikely from the degree of recovery that the collateral circulation could have been entirely responsible. I do not know whether arterial spasm of such duration is possible without permanent arterial occlusion. The relief of tension produced very striking improvement.

A photograph taken on Oct. 27 illustrates the extent and boundaries of the lesion.

Kent and Sussex Hospital,
Tunbridge Wells. ERIC FOWLER.

CATHETER DRAINAGE AND INFECTION IN ACUTE RETENTION OF URINE

SIR,—I have read with interest the letters from Mr. Ashton Miller and Dr. Harrison (Feb. 20 and 27) about the use of the ' Portex ' Gibbon catheter. A modification of this catheter, designed by Mr. A. Walsh, of Dublin, has now been developed for use after prostatectomy. This is of larger bore than the standard Gibbon catheter, with facilities for bladder irrigation, and effectively overcomes the disadvantages mentioned by Mr. Miller (Feb. 27).

D. E. STEELE
Hythe, Kent. Medical Adviser, Portland Plastics Ltd.

REJECTION OF RENAL HOMOGRAFTS

SIR,—In his interesting report of Feb. 20 Mr. Calne observed that 6-mercaptopurine abolished the immature plasma-cell reaction in homotransplanted kidneys. This was surely to be expected since the drug will act on the reticuloendothelial system of both the host and the transplant. The same applies to cortisone which also can abolish the immature plasma cells without, however, prolonging survival.[1] Local X-irradiation of the kidney prior to transplantation can also abolish the development of the immature plasma cells.[2] These cells have failed to appear in a kidney transferred from a donor of bone-marrow to a total-body-irradiated dog.[3]

That the immature plasma cells evolve from reticulum cells in the homotransplanted kidney has convinced few people.[4] The evidence now is that these cells can be prevented from appearing in kidneys transplanted to dogs treated with cortisone and 6-mercaptopurine, and also by local X-irradiation of the kidney prior to transplantation. The conclusion drawn from the results obtained from the first and last agency was that the immature plasma cells were not responsible for the disintegration of homotransplanted kidneys.[1]

There is a hint in the report of primary anuria, and this I take to be type-1 anuria which has already been fully described.[5]

It is gratifying to find that Mr. Calne has given up bilateral nephrectomy at the time of the transplant operation. The advantages of unilateral nephrectomy in kidney transplantation experiments have already been stressed.[6]

If one wishes to apply severe measures, such as total-body irradiation and 6-mercaptopurine, to dogs special postoperative care must be ensured. In addition to antibiotics, a special room, well heated and sterilised by ultraviolet light, is essential if the dogs are not to die of intercurrent infections. This precaution might allow 6-mercaptopurine treated dogs to survive

1. Dempster, W. J. *Arch. int. Pharmacodyn.* 1953, **95**, 253.
2. Dempster, W. J. *Brit. J. Surg.* 1953, **40**, 447.
3. Mannick, J. A., Lochte, H. L., Ashley, C. A., Donnall Thomas, E., Ferrebee, J. W. *Surgery*, 1959, **46**, 821.
4. Darmady, E. M., Dempster, W. J., Stranack, F. *J. Path. Bact.* 1955, **70**, 225.
5. Dempster, W. J. *Acta med. scand.* 1954, **148**, 91.
6. Dempster, W. J. *ibid.* 1953, **144**, 360.

longer than 47 days which is very encouraging, although little prolongation of survival has attended skin homografts. It should be realised, however, that any measure, so far as one can see at the moment, which can suppress the homograft rejection process must also render the host an immunological cripple.

It is stated that the kidneys which survived for 21 and 47 days respectively were concentrating. I would accept that for the 47-day survival but not for the 21-day survival. It has been fully demonstrated that kidneys in the pelvis do not concentrate for the first three weeks or so.[7 8] The data for concentrated dog urine are not given, but it should be realised that the normal concentration is 1·030–1·050.

Department of Experimental Surgery,
Postgraduate Medical School,
London, W.12. W. J. DEMPSTER.

AGRANULOCYTOSIS ASSOCIATED WITH IMIPRAMINE

SIR,—We lately observed agranulocytosis in a patient whose treatment had included imipramine ('Tofranil').

A woman of 72 was admitted to Hellesdon Hospital on May 25, 1959, with three weeks' history of depression and agitation. She had been treated thirty years previously in a mental hospital for a depressive illness but had since been quite well until the present attack. She was thought to be suffering from mild congestive heart-failure due to hypertensive and ischæmic heart-disease; and digitalis folia and *Rauwolfia canescens* ('Harmonyl') were given. Œdema subsided and she became ambulant, but was still very depressed. On June 29, 1959, treatment was begun with imipramine (50 mg. t.d.s.), and sodium amylobarbitone (gr. 3) was given when necessary. Her mental state improved considerably until Aug. 12, exactly forty-five days after imipramine was first administered, when sore throat, stomatitis, and a fever of 103°F developed. A white blood-count was 600 per c.mm. (84% lymphocytes, 16% monocytes, and no granulocytes). Rauwolfia and imipramine were discontinued, and penicillin was commenced. A swab from the mouth grew a coagulase-positive staphylococcus and monilia. She was transferred to the Norfolk and Norwich Hospital on Aug. 15.

She was a withdrawn ill-looking woman with a fever of 101·8°F, a pulse-rate of 90, and a tachypnœa of 26. There were many large necrotic ulcers scattered over the tongue, buccal mucosa, gums, palate, tonsils, and pharynx, and the whole of the oral mucous membrane was red and inflamed.

Investigations on the day of admission were:

Hæmoglobin 78%, white cells 700 per c.mm. (neutrophils 1%, lymphocytes 80%, monocytes 17%, atypical mononuclear cells 2%), erythrocyte sedimentation-rate 83 mm. in 1 hr. Direct Coombs test negative.

In the sternal marrow the red-cell series were quite normal. The megakaryocyte count was normal but there were a few bizarre forms with multilobed nuclei. There were a few scattered progranulocytes but no other cells of the white-cell series were seen. Plasma cells were slightly increased in number. The picture was one of complete agranulocytosis.

Penicillin was continued and prednisone given in large doses. But the white count fell to 240 per c. mm., bronchopneumonia developed, and she died on the seventh day after admission. Apart from bronchopneumonia, and some aortic valvular sclerosis, no other abnormality was found at necropsy.

Abnormalities in the white-cell series have been reported in association with imipramine, including transient eosinophilia,[9] leucocytosis,[10] and leucopenia, but no previous fatal agranulocytosis has been recorded.

Structurally, imipramine may be compared with the phenothiazene derivatives, in which the benzene rings are linked by a sulphur atom: in imipramine this is replaced by an ethylene group. Leucopenia and agranulocytosis has often followed the administration of phenothiazine derivatives and the picture seems rather similar to the one described above.

Our patient received only sporadic doses of amylobarbitone and it seems extremely unlikely that this caused her condition; and *Rauwolfia canescens*, which is widely used in psychiatric practice and has been given major trials as a hypotensive agent, has so far not been incriminated as a cause of agranulocytosis.

We wish to thank Dr. A. Batty Shaw and Dr. F. J. Napier for their kind permission to report this case.

Norfolk and Norwich Hospital. J. A. MORGAN-HUGHES.
Hellesdon Hospital, Norwich. I. N. S. HEALD.

7. Dempster, W. J., Joekes, A. M., Oeconomos, N *Ann. R. Coll. Surg. Engl.* 1955, **16**, 324.
8. Murray, J. E., Lang, S., Miller, B. F., Dammin, G. J. *Surg. Gynec. Obstet.* 1956, **103**, 15.
9. Hippius, H. *Canad. psychiat. Ass. J.* 1959, **4** S, 182.
10. Moll, A. E. *ibid.* p. 64.

SPREAD OF STAPHYLOCOCCI FROM HOSPITAL TO COMMUNITY

SIR,—In your annotation of Feb. 20 you suggest that the spread of staphylococci from maternity hospitals into the community may be reduced by the use of disinfectants which diminish the staphylococcal colonisation of infants in the hospitals. We have recently confirmed this by investigating the nasal carriage of *Staphylococcus aureus* by infants and mothers, 6–8 weeks after leaving hospital.

There were two nurseries in which the routine procedures were similar except that, in one, hexachlorophane powder was frequently applied to the infants' skin as we have described,[1] and, in addition, 'Naseptin' cream (containing neomycin and chlorhexidine) was applied once daily to their anterior nares.

Of 87 infants who had been in the control nursery, 38 (44%) were carrying penicillin-resistant staphylococci and 27 (31%) sensitive staphylococci, compared with 22 (17%) and 21 (17%) of 127 infants who had been in the treated nursery.

Of 110 mothers of infants who had been in the control nursery, 29 (26%) were carrying penicillin-resistant staphylococci and 49 (45%) were carrying penicillin-sensitive staphylococci, compared with 14 (9%) and 52 (34%) of 153 mothers of infants from the treated nursery. The nasal carrier-rate in mothers of infants who had been in the treated nursery differed very little from the rate in mothers on admission to hospital.

Department of Pathology,
Bristol Royal Hospital,
Royal Infirmary Branch,
Bristol, 2.

BARBARA DONNISON
W. A. GILLESPIE
K. SIMPSON
ROSEMARY C. TOZER.

CHILDREN IN POINTED SHOES

SIR,—I should like to draw attention to the ill effects of shoes with pointed toes upon the feet of little girls of as young as 12 years. Any fond but foolish mother may now provide them for her daughter. It is shameful that this execrable fashion of the '20s should ever have been revived for adult women (and, surprisingly, even for men!) let alone imposed on little girls.

I have recently seen girls with severe hallux valgus and toe deformity from this cause. The pliable growing bones of children are obviously vulnerable to pressure from such an unphysiological shape. The shoe assistant's stock remark seems to be that "the foot does not go into the pointed toe". Since the toe-point is not blocked out, the effects of weight-bearing must be to force the toes well within the pointed cavity.

The Chinese custom of foot-binding rightly resulted in much indignation in the past. May I suggest that pointed shoes for children are only one degree removed from this practice?

It is sad to see the careful work of certain shoe manufacturers and others, in ensuring a good range of fittings for children, thus set back by the irresponsibility of some manufacturers, retailers, and the general public.

London, W.5. PAMELA AYLETT.

1. *Brit. med. J.* Jan. 30, 1960, p. 315.

Parliament

Hospital Buildings

ON Feb. 29, in a written answer, the Minister of Health announced that he had asked hospital boards to bring to completion the planning of a number of additional major projects.

These include work on a number of new hospitals. There is the first phase of a new teaching hospital in Liverpool, a new maternity hospital to replace the Birmingham Maternity Hospital, and a new building for the Tavistock Clinic. There are further stages of the new general hospitals for Crawley and Truro, and the completion of those for Harlow and Huddersfield, and of the mental deficiency hospital at Oakwood Park, Conway.

The list also includes the first phase of the redevelopment of the Gloucestershire Royal Hospital and a further stage of the development of the Poole General Hospital.

New maternity departments are proposed at the Norfolk and Norwich Hospital, Ashton-under-Lyne General Hospital, Burnley General Hospital, Chester City Hospital, Margate General Hospital, and Watford. An obstetric unit will form part of a large development at the New Cross Hospital and Royal Hospital at Wolverhampton, and there will be a new outpatient department at Queen Charlotte's Hospital.

There will be a new ophthalmic block at the Royal Berkshire Hospital, Reading, and a neurosurgical unit at Walton Hospital to serve the Liverpool hospital region.

Large developments proposed at other hospitals include: a surgical block at Derby City Hospital, an operating-theatre suite and diagnostic radiology department at the Prince of Wales's Hospital, Tottenham, a new outpatient department for St. John's Hospital, Battersea, and extensions to the Southend General Hospital. There will be a new ward block at the Christie Hospital, Manchester, extensions to the Scalebor Park Mental Hospital at Burley-in-Wharfedale, and improvements to St. George's Mental Hospital, Morpeth. The engineering services at St. John's Hospital, Stone, are to be modernised, and new boilers and laundry are included for the Newcastle General Hospital.

The cost of these schemes is likely to be about £20 million.

Public Health Laboratory Service Bill

At the report stage of this Bill in the House of Lords on Feb. 29 the constitution of the proposed Public Health Laboratory Service Board was amended to include not less than one member representing the hospital service and not less than one general practitioner. The appointment of the chairman remains at the discretion of the Minister of Health, but he need not necessarily be medically qualified.

QUESTION TIME

Domiciliary Consultative Service

Sir GODFREY NICHOLSON asked the Minister if he would summarise the replies he had received from regional hospital boards in answer to his request of February, 1959, that they should give him the factual information on which he could base a decision whether to institute an inquiry into the operation of the domiciliary consultative service; and how this information compares with the evidence from hospital authorities reported by the Select Committee on Estimates of 1956–57.—Mr. WALKER-SMITH replied: The replies from boards revealed little information indicating abuse of the service, and in such rare or doubtful cases as transpired action was take with a view to putting it right. The replies also revealed the difficulty of obtaining factual information of any abuse in present circumstances. As this aspect of the consultant services among others was before the Royal Commission on Doctors' and Dentists' Remuneration, I decided to await their report before proceeding; and now that the report has been received, I shall consider what action is appropriate in this as in other respects.

University Entrants

The numbers of autumn-term new entrants to the universities and university colleges in Great Britain in 1957, 1958, and 1959 were 27,206, 27,757, and 27,533 respectively. The University Grants Committee estimates that new entrants in 1960, 1961, and 1962 will number 29,500, 31,000 and 32,000 respectively.

Convalescent Information Bureau

A meeting is to be held on March 17 to discuss with the regional hospital boards a proposal to establish a bureau for the London region to advise on the placing of patients in need of convalescent treatment. This was one of the recommendations of the Working Party on convalescent treatment.

Obituary

WILFRED JOHN HARRIS

M.D. Cantab., F.R.C.P.

Dr. Wilfred Harris, consulting physician to St. Mary's Hospital and the Maida Vale Hospital for Nervous Disease, died in London on Feb. 28 at the age of 90.

The son of Surgeon General W. H. Harris, I.M.S., he was born in Madras, and he was educated at Sherborne School, University College School, and Cambridge, where he took the natural sciences tripos in 1891. He qualified from St. Mary's in 1894. After holding house-appointments at the National Hospital, Queen Square, he joined the staff of the Maida Vale Hospital in 1903 and of St. Mary's two years later. He was elected F.R.C.P. in 1905, and he examined in medicine for the college and for the universities of Cambridge and Durham. His book on *Electrical Treatment* appeared in 1908. His other publications included *Nerve Injuries and Shock* (1915), *Neuritis and Neuralgia* (1926), *The Facial Neuralgias* (1937), and *Morphology of the Brachial Plexus* (1939). He held office as president of the Association of British Neurologists, and of the British branch of the International League against Epilepsy.

Lafayette

W. R. B. writes:

" Harris was on the house at the National Hospital, Queen Square, in the days when Hughlings Jackson and Gowers were on the staff. Having joined the staff of St. Mary's and the Hospital for Epilepsy and Paralysis, Maida Vale, as it was then called, he soon became known for his development of the technique of alcoholic injection of the gasserian ganglion and the divisions of the trigeminal nerve for trigeminal neuralgia. He was extremely skilful at this and continued doing it until he was over 80. Though by nature a somewhat impatient man, his technique was based upon great patience, dexterity, and an intuitive visualisation of the individual anatomy of each patient, derived from great experience. In a demonstration at the International Neurological Congress in 1935 he achieved the tour-de-force of picking out by injection the fibres of the second division alone within the ganglion. His interest in facial pain naturally extended to its diagnostic problems, and led him to describe the paroxysmal type of headache, which he called ' migrainous neuralgia ', and the intractable form of facial pain often seen in women, for which he coined the term ' psychalgia '. His book on *Neuritis and Neuralgia* is still worth reading for the wealth of clinical experience it embodies, and is perhaps none the worse for its somewhat anecdotal style. Though devoting much time to the exacting demands of his special interest, Harris was a good all-round clinical neurologist, and his observations at the monthly staff clinical meetings at Maida Vale were always worth listening to. One of his earliest interests was the comparative anatomy of the nervous

system, and he worked for many years in his spare time at the Zoo dissecting the brachial plexus in reptiles, birds, and mammals, and published his results in a monograph on *The Morphology of the Brachial Plexus.*

"Harris established at Maida Vale one of the first occupational therapy units in this country. He was devoted to 'Maida', as he called it, and during the war, when younger members of the staff were away, he took up outpatient work again, though he was over 70. His long reign as senior physician—there was no retiring age then, and he went on till he was 75—seemed to mellow him, and bring out the genial and humorous side of his character. He was a keen follower of the St. Mary's rugger team, played golf, collected old silver and drove his car with abandon."

Dr. Harris married in 1906, Mabel, daughter of the late Rear-Admiral Richard Mayne, who survives him with two sons and a daughter.

JOHN CHARLTON BRISCOE

Bt., M.D. Lond., F.R.C.P.

Sir Charlton Briscoe, consulting physician to King's College Hospital, London, died on Feb. 28 at his home in Suffolk. He was 85 years of age.

The second son of Sir John Briscoe, the first baronet, who was a former high sheriff of Cambridgeshire, he succeeded to the family honours on the death of his elder brother in 1921.

K. C. H. Gazette

From Harrow, Briscoe entered the medical department of King's College in 1892. He qualified in 1898 and the same year was appointed house-physician at King's College Hospital to David Ferrier. A contemporary later recalled:

"I first met Briscoe when I started as a clerk to Sir David Ferrier, whom Briscoe accompanied on his ward rounds, dressed in a beautiful frock-coat. In those days, which were supposed to be frivolous—days which are now spoken of as the 'naughty 'nineties' —all H.P.s wore frock-coats for their rounds, and so did the H.S.s and very dignified they all looked. White coats were introduced during the Boer War."

Later Briscoe became Sambrooke registrar at King's, and after postgraduate study at Göttingen under Aschoff he returned to King's in 1903 as senior medical tutor and registrar. In 1908 he was appointed assistant physician and two years later he became pathological registrar. About this time he also acted for a session as dean of the medical school. In 1915 he became a full physician. He also held appointments at the Evelina Hospital and the Hospital of St. John and St. Elizabeth. During the 1914–18 war he served as a major in the R.A.M.C., and he was vice-president of the Ministry of Pensions special medical board for shellshock.

Briscoe was elected F.R.C.P. in 1910 and he served the college as a councillor and censor. In 1927 he delivered the college's Lumleian lecture, speaking on muscular mechanisms of respiration. This subject was the centre of his clinical and experimental research, and his other published work included papers on the phagocytic action of the alveolar cells of the lungs, the mechanism of post-operative massive collapse of the lungs, anginal syndrome, and unilateral phrenic-nerve paralysis. When he retired in 1935 he was senior physician at King's.

Of these years, J. L. relates:

"Some years before he retired Sir Charlton had acquired Lakenheath Hall, a thatched house set in a large garden with some hundreds of acres of heath. This was virtually barren land and it was a challenge to Briscoe. With his scientific background he started experimenting with fertilisers and unusual crops, and by dint of hard work and patience the soil gradually began to be productive and yield crops of oats, sugar beet, and other root-crops, not to speak of asparagus, to the surprise of some of the local farmers. He bred and developed a herd of pigs and fattened beef on the fields which had once been rough heath. He was a keen shot and his ventures in farming gave cover for his birds, so that the pheasants and partridges throve well and gave good sport to his guests.

"Sir Charlton became the village squire with all the duties and responsibilities entailed, and he and Lady Briscoe did much for the life of the village. He was a justice of the peace and for many years was a member of the Ouse Conservancy Board. He underwent a major operation at the age of 78, which he accepted with his usual sang-froid, and returned to his active life within a remarkably short time. Many of his old students and colleagues enjoyed weekends at Lakenheath, where they were expected to take an active interest in pigs and crops with their host, and in archæology with their hostess, who had made many discoveries in the neighbourhood.

"Johnnie Briscoe or Sir Charlton, according to the seniority of his friends, was a man who inspired affection. When he attended the annual hospital dinner he would be surrounded by a crowd of his old students, all delighted to be with him. He was an outstanding physician and teacher, a responsible landowner and a man of probity, but above all he was a man everyone loved."

C. N. writes:

"Sir Charlton Briscoe was a much more remarkable man than most of his contemporaries suspected. They may have thought that he owed his position to an inherited title: they may have been unimpressed by a big, quiet, rather reserved man who never set out to be a spectacular doctor: they may have overestimated his dislike of teaching and they may have thought his mind was occupied with rather dull researches.

"The interesting fact is that, forty years later, many of his students who were in the hospital in his time would agree that the things they remember now are the things that originated with him, and that his status has steadily increased in their estimation over the years, while that of the contemporarily more popular teachers has declined. At the bottom of it all is the fact that Sir Charlton was not brilliant but of immense intellectual solidity. That kind of man is not showy: everything he said was the result of thoroughly tested experience. This made him a sound clinician and a sensible therapist. He could occasionally do remarkable things: once, in the 1920s when (as a chest physician) he was asked to advise about a young woman with a pleural effusion, he said meditatively: 'You know, I don't believe this is T.B. at all. She looks very like typhoid used to look like in 1900: you might do a Widal'. It was, of course, positive. But he was the last person to indulge in spot diagnosis, because he was a very careful collector of scientific evidence. He shared a research laboratory with Lenthal Cheatle and Arthur Whitfield and year after year made records of the movements of the individual respiratory muscles, from which he developed a clinical technique of assessing their functional activity, and formulated the explanation of the mechanism of chest pains, including that of angina, in a series of researches now forgotten but which were of monumental solidity and will one day be rediscovered. It was the same solidity of the observed background which made his advice on treatment so successful. He had little belief in the ordinary drug treatments of his day and this led him to apply a great deal of treatment by simple dietetic and physical means which are as sound now as they were then.

"Add to this that he was a sterling character. He was a gentleman if ever there was one, transparently straight and honest. And a human being: he was a student when King's was going through a rather full-blooded period, and Sir Charlton was, from all accounts, a fairly full-blooded student. He was a big enough man for this to make him sympathise

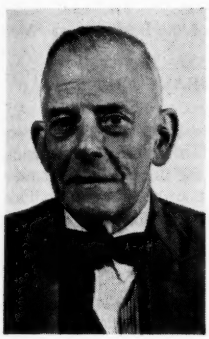
with, rather than condemn, the students of a younger generation."

Sir Charlton married in 1910 Dr. Grace Stagg, who survives him with their two sons.

SYDNEY ALEXANDER HENRY

M.A., M.D. Cantab., F.R.C.P., F.R.C.S., D.P.H., D.T.M., D.I.H.

Dr. S. A. Henry died in London on Feb. 13 at the age of 79. For twenty-four years he was one of H.M. medical inspectors of factories, and he was well known as an authority on occupational cancer.



Born in Rochdale, the son of Dr. Joseph Henry, he was educated at Rossall School, Trinity College, Cambridge, and St. Thomas's Hospital, London. After qualifying in 1905 he spent a few years as an assistant school medical officer to Dr. J. C. Bridge in Breconshire. He then went into general practice in Rochdale, where he also held the post of certifying factory surgeon. In this capacity he met Sir Thomas Legge, with whom he developed a close friendship. In 1920 Henry joined the Factory Department of the Home Office, and thus began a close association with Legge and with Bridge, who had joined the Factory Department some years previously.

For ten years Henry worked in Manchester, and during this time he became secretary of two departmental committees—one on mule-spinners' cancer and the other on dust in cotton cardrooms. On both committees he served with conspicuous success, as well as carrying out his multifarious official duties. But his greatest interest was in occupational cancer, and many of his long list of publications are on this subject. His book on *Cancer of the Scrotum in Relation to Occupation* (1946) showed his meticulous attention to detail, and his terrier-like persistence in tracing the occupational histories of people who had died from this disease. He also wrote about occupational cancer of the bladder, prostate, and skin.

He delivered Hunterian lectures to the Royal College of Surgeons of England in 1940 and 1950, and the Milroy lectures to the Royal College of Physicians in 1943. He was elected F.R.C.P. in 1945. He endowed college lectureships in memory of his parents—the Joseph Henry lecture at the Royal College of Surgeons and the Ernestine Henry lecture at the Royal College of Physicians.

A. I. G. McL. writes:

"Henry had a passion for collecting, not only degrees and diplomas, but also first editions, china, paintings, and prints of the French Impressionists, as well as early photographs and engravings of chimney-sweeps, and in fact anything which appertained to and which threw light on occupational cancer. Lady Legge gave Henry many of the specimens which Legge had collected, and these were presented to Manchester University as the Legge collection. His own collection of specimens, photographs, and documents concerning chimney-sweeps was given to the Leeds Municipal Museum.

"Henry was enthusiastic, charming, and a voluble conversationalist. His preoccupations made him absent-minded, and many amusing stories are current in the Factory Department about this aspect of his personality. It was almost impossible to steer him past a bookshop, and once he began browsing amongst books he would forget all his appointments. His friends will remember with affection his amiable eccentricities, but they also realise that his pioneer work on occupational cancer will stand the test of time."

JOHN DOCKRAY

M.B. Cantab., F.R.C.P.

Dr. Dockray, physician to the Royal Isle of Wight County Hospital, died on Feb. 21 at the age of 59.

He was educated at Trinity College, Cambridge, and St. Bartholomew's Hospital, London, qualifying in 1925. After holding house-appointments in London at Barts and the Royal Chest Hospital and in Cambridge at Addenbrooke's Hospital, he was for a short time personal physician to the Crown Prince of Siam. He settled in general practice at Ryde in 1931 and two years later was appointed physician to the Royal Isle of Wight County Hospital. He remained in general practice until the start of the National Health Service in 1948, when he became a consultant physician. He was a member of the Isle of Wight hospital management committee and the western area committee of the South West Metropolitan Regional Hospital Board, now the Wessex Regional Hospital Board. He was elected F.R.C.P. in 1950.

T. C. H. writes:

"John Dockray had many facets. Though he naturally generated a warm glow of friendship, he could occasionally be a hardheaded Lancastrian. He did not encourage intimacy, but all his patients adored him. He had a diffident, almost shy, manner. His speech was slow with a slight hesitation, nearly a stutter, which gave added emphasis to what he said.

"He was a general practitioner turned consultant, but even as a consultant he was more interested in patients than diseases. He had a passion for detail. No patient could be radiologically examined unless Dockray was present. The laboratory investigations had to be earnestly discussed with the pathologist. Prescriptions had to be written in his own hand. Nothing was too much trouble. Time was of no account. He was always working. His private life hardly seemed to exist. His kindliness was all-pervading. For several years he took a lonely old man on his visits round the island. At Christmastime everyone in the hospital from the wardmaid upwards must have a present. Who but he could have produced an egg from his pocket for a visiting consultant's tea? It was quite in character that his last act, when already very ill, was to buy a potted azalea for the room of a new house-physician.

"He never claimed profound knowledge, but wisdom he had in superabundance. No-one could weigh up a difficult medical situation or an administrative problem better than he. He naturally gravitated to committee work, until latterly it almost filled his whole life. Everyone asked his opinion and his judgment was unerring.

"St. Bartholomew's Hospital (where he was Lord Horder's house-physician) and Cambridge University were perhaps the places he loved most. Once, when driving through Cambridge, he committed a minor traffic offence. He sent a blank cheque to the magistrates saying he had such happy memories of his undergraduate days that they could fill in whatever sum they liked. Inevitably legends grew up round him. Is it true that, virtually a teetotaller and non-smoker, he had a fine collection of old brandy and cigars? He had a quiet interest in games. His summer holiday always coincided with Wimbledon and the test match, and he played tennis every Sunday afternoon. He travelled to Helsinki for the Olympic Games, and he would probably have been at Rome this year. As a young man he had been a keen rugger player, a prop forward one would suspect; and as a prop, a solid four-square figure, he has been leaned on ever since. Now there is only a great empty space."

Dr. Dockray is survived by his widow.

Appointments

FRANCIS, A. E., M.D. Lond., M.R.C.P.: consultant bacteriologist, St. Peter's Hospital, London.

HANLEY, J. A., M.CH. N.U.I., F.R.C.S.: consultant surgeon, The Sheil Hospital, Ballyshannon, Donegal, Eire.

LLOYD, V. A., M.B. Birm., D.P.H.: deputy M.O.H. and deputy principal school M.O., Smethwick.

MACFARLANE, D. A., M.CH., B.SC. Wales, F.R.C.S.: consultant surgeon, Princess Beatrice and St. Stephen's Hospitals, London.

MITCHELL-HEGGS, G. B., O.B.E., M.D. Lond., F.R.C.P.: honorary dermatologist, Hospital of St. John and St. Elizabeth, London.

Notes and News

A COLLEGE CONFERENCE

THE Royal College of Physicians of London have chosen Recent Advances in Renal Disease as the subject of their next conference, which is to be held on July 22 and 23.

Prof. R. A. McCance will take the chair at the first session, when Prof. D. A. K. Black, Dr. O. M. Wrong, and Dr. A. M. Joekes will speak on renal function and structure, and Dr. M. D. Milne and Dr. R. C. Jackson on acute renal failure. Lord Evans will be in the chair in the afternoon, when Prof. J. R. Squire, Dr. Philip Freedman, Dr. L. W. Loughridge, Prof. G. A. Smart, and Dr. W. W. Holland will discuss the nephrotic syndrome. On Saturday, the 23rd, Sir Robert Platt, the president, will be the chairman at the morning session, at which the speakers on pyelonephritis will be Prof. M. L. Rosenheim, Dr. D. Edwards, and Dr. H. E. de Wardener. Prof. C. E. Dent and Dr. S. W. Stanbury will speak on metabolic aspects of renal disease. In the afternoon Prof. John McMichael will take the chair at a session on hypertension and the kidney at which the speakers will be Dr. C. J. Hodson, Dr. A. G. Spencer, Prof. Clifford Wilson, and Mr. Kenneth Owen.

Like the earlier college conferences the meeting is primarily arranged for fellows and members who are consultants in medicine or pathology. Numbers may be limited and early applications should be made to the registrar at the college, Pall Mall East, S.W.1. The entrance fee of 5 guineas (which includes lunches and dinner) should accompany the application.

REGALIS SOCIETAS

THE charter conferring this title was granted by Charles II in 1662, and he was honouring the society formed two years earlier " for the promoting of Physico-Mathematicall Experimentall learning ". This year the tercentenary of the Royal Society will be celebrated on July 18–26 in London, Oxford, and Cambridge. Announcing the arrangements last week, Sir Cyril Hinshelwood, the president, hoped that this summer the society would be able to bridge the gap between Science and the Public.

The plans include tercentenary lectures by ten fellows, who will present some of the major achievements of modern British science; visits to many laboratories to enable those from overseas to see something of current research; and a special conversazione with exhibits reviewing British scientific progress of the past ten years or so. At a banquet on July 26, the Prime Minister will propose The Society.

A special issue of the society's *Notes and Records*, edited by Sir Harold Hartley, will deal with the origins of the society; and Prof. E. N. da C. Andrade has prepared a brief history, to be supplied to all attending the celebrations. The year is also marked by the appearance of the first of seven volumes of *The Correspondence of Isaac Newton*, the work of a committee led by Professor Andrade, and other volumes are expected to be ready before July.

A NEW UNIT FOR CARDIOVASCULAR SURGERY

THE new cardiovascular-surgery unit at Glasgow Royal Infirmary was opened on Feb. 26 by Mr. Thomas Galbraith, joint parliamentary under-secretary of State for Scotland. He referred to it as a milestone on the journey of the team led by Prof. W. A. Mackey towards perfecting the use of heart-lung machines. He congratulated members of the Scottish Hospital Endowment Research Trust on their support which had made possible the purchase of the heart-lung machine. The new unit had also received support from the University, the hospital authorities, and the Royal Infirmary board of management's own endowment fund, thus illustrating the widespread support for medical research in the hospital service in Scotland today.

Mr. Galbraith added that there was to be a substantial programme of teaching-hospital development, in which the Royal Infirmary of Glasgow would have its share. It was planned eventually to rebuild completely four out of Scotland's six teaching hospitals and to make extensive additions to two others—a programme eventually costing as much as £15 million, which would ensure that Scottish doctors in teaching hospitals had facilities equal to any in the world.

JOHNS HOPKINS

Mark Twain, when given a degree at Johns Hopkins University in the year 1898, is said to have expressed concern over the mis-spelling in its name. He feared lest the people of Baltimore would lose confidence in the organisers of their college if they could not spell " John " correctly!

The reason for the unusual name has lately been explained.[1] Johns Hopkins (1795–1873), who founded both the university and the hospital, was the great-grandson of Gerard Hopkins, Jr., whose father had landed as an immigrant at Chesapeake Bay in the year 1640. Gerard Hopkins, Jr., married Margaret, daughter of Richard Johns, of Bristol, who had settled in Maryland in 1675. It was in this way that the name Johns was introduced into the Hopkins family. The first Johns Hopkins, grandfather of the founder of the hospital, was born in 1720.

SOCIETY OF ST. MARGARET (EAST GRINSTEAD) APPEAL

THE Hostel of God (a free home for the dying at Clapham Common), St. Joseph's Hospital for Incurables at Chiswick, and St. Catherine's Home, Ventnor, for delicate children are open to all without distinction of creed or country, and all are under the care of the Sisterhood of St. Margaret, East Grinstead. An appeal has been launched on behalf of this Anglican community, which, for over a hundred years, has given devoted service to the sick and aged and to children.

All the Sisters are trained at St. Margaret's Convent, East Grinstead, which is now nearly a century old. Essential repairs and rebuilding will cost about £12,000. Under the rules made by the founder in very different times no endowment is permitted; so there are no funds to meet emergencies. Last year the Sisters had to be withdrawn from three homes for elderly ladies because of financial difficulties.

The honorary treasurer of the appeal fund is Mr. N. Dru Drury, Millfield, Burwash, Sussex.

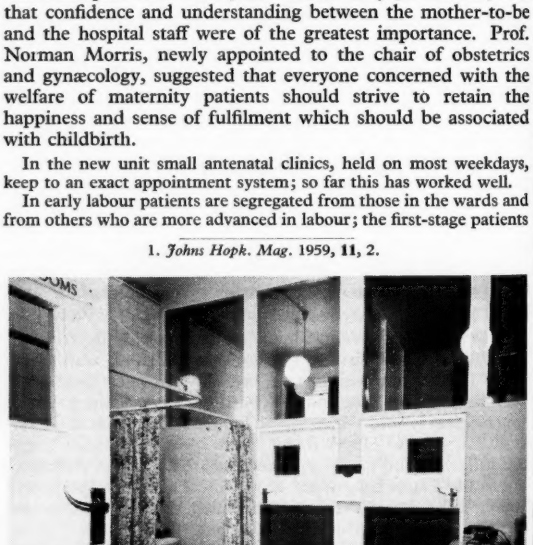
OBSTETRIC UNIT AT CHARING CROSS

AT the official opening of the new obstetric unit at Charing Cross Hospital on Feb. 23, Sir Andrew Claye, P.R.C.O.G., said that confidence and understanding between the mother-to-be and the hospital staff were of the greatest importance. Prof. Norman Morris, newly appointed to the chair of obstetrics and gynæcology, suggested that everyone concerned with the welfare of maternity patients should strive to retain the happiness and sense of fulfilment which should be associated with childbirth.

In the new unit small antenatal clinics, held on most weekdays, keep to an exact appointment system; so far this has worked well.

In early labour patients are segregated from those in the wards and from others who are more advanced in labour; the first-stage patients

1. *Johns Hopk. Mag.* 1959, **11**, 2.



The first-stage suite.

are thus given some privacy, but they are supervised continuously by a midwife, and their husbands are encouraged to stay with them.

The labour-ward has two separate rooms, one of which can be used as an operating-theatre when necessary. The other has a two-way mirror which allows students to observe a delivery from outside the room, or the mother to watch her baby being born.

A colourful day-room helps to encourage early ambulation. The bathrooms are fitted with showers and bidet suites.

To reduce cross-infection the floors have been treated with a self-curing plastic which completely seals the surface. The covers of cleaning implements are impregnated with material which attracts dirt but does not leave a streaky film. Both this, and the special paint, are claimed to have fungicidal and bactericidal properties.

Because the entire Charing Cross Hospital is soon to be rebuilt at Fulham these alterations have been made as economically as possible.

MENTAL HEALTH INFORMATION SERVICE

IN New York, between 9 A.M. and 5 P.M., by dialling LA4-7719 one can get information about almost any kind of psychiatric service [1] from a psychiatric social worker in the Manhattan Society for Mental Health. She can advise callers about waiting periods for treatment at clinics and about the legal aspects of commitment, and can reassure people who have frightening misconceptions about mental hospitals. Last year the service received 4400 telephone calls, as well as many letters and visits. Almost half the calls are from people who seek help for themselves.

HOSPITAL COSTS

HOSPITAL Costing Returns [2] for the year ended March 31, 1959, published last week, cover all National Health Service hospitals in *England and Wales*, other than some 250 large hospitals whose detailed departmental costs were published last November. These latest returns, which relate to the second year of revised costing arrangements, are an improved version of those published for periods prior to April 1, 1957. They show for each hospital the net average inpatient cost per week, and (except for hospitals where patients remain for long periods) the net average inpatient cost per case. In addition, the principal direct expenses (such as salaries and wages and materials) of individual departments are expressed in terms of cost per unit of work performed. The cost unit depends on the function of the department: catering department costs, for example, are expressed as cost per person fed per week.

The following figures show certain national average costs for 1958–59, with comparative figures for 1957–58, for all hospitals in England and Wales (*including* the 250 large hospitals for which separate returns were issued):

Classification of hospital	*Net inpatient cost per week* Year ended March 31 1958	1959	*Net inpatient cost per case* Year ended March 31 1958	1959
	£ s. d.	£ s. d.	£ s. d.	£ s. d.
Non-teaching hospitals:				
Acute:				
1–50 beds	21 3 1	22 9 11	40 12 11	43 3 11
101–300 beds	23 14 7	24 14 7	46 6 0	48 5 7
Mainly acute	19 5 10	20 11 0	56 11 11	58 11 11
Chronic	9 9 5	10 4 0	.. ..	.. ..
Maternity	23 2 4	24 12 7	36 3 1	37 4 4
Mental illness	6 8 11	6 19 2	..	..
Mental deficiency	6 2 1	6 8 0	..	..
Tuberculosis and chest	16 14 3	18 6 5	.. ..	.. ..
Children (acute)	22 12 0	24 17 5	47 9 1	48 9 5
Teaching hospitals:				
Acute:				
(*a*) London	33 4 2	34 9 5	77 12 10	80 3 2
(*b*) Provinces	27 10 1	28 13 10	52 7 9	54 19 10

The average weekly cost of maintaining a patient in medium-sized (51–300 beds) general hospitals in *Scotland* during the year ended March 31, 1959, was £20 1*s.* 6*d.*[3] For major teaching general hospitals the average weekly cost per inpatient was £21 12*s.* 6*d.* These are the net costs per inpatient, including the cost of specialist services, but excluding outpatient expenditure. The average inclusive cost of each outpatient attendance was 10*s.* 8*d.* and 11*s.* respectively in the medium-sized and the major teaching general hospitals. The average daily number of inpatients in hospitals of all types was 53,843 and the total number of outpatient attendances was 5,642,899.

The average costs per inpatient per week in other types of Scottish hospitals were:

	£ s. d.
General:	
Over 300 beds	20 12 6
Up to 50 beds	17 10 5
Chronic sick	10 18 6
Convalescent	10 4 0
Sanatoria	16 14 3
Isolation and tuberculosis	18 14 5
Maternity	25 3 2
Mental	7 7 8
Mental deficiency	6 7 4

Of every £1 spent on maintaining and treating a patient in a Scottish hospital, 11*s.* 9*d.* was spent on the salaries and wages of medical, nursing, and other staff, 5*s.* 5*d.* on supplies including provisions, drugs, dressings, and boiler fuel, and 2*s.* 10*d.* on a wide range of services such as laundry, building maintenance, rates, postages, and telephone.

1. *New York Times*, Feb. 21, 1960.
2. National Health Service Hospital Costing Returns, Year ended 31st March, 1959. Volume II (Hospitals which operated the Alternative Scheme). H.M. Stationery Office. 32*s.* 6*d.*
3. Department of Health for Scotland. Analysis of Running Costs of Hospitals, Year ended 31st March, 1959. H.M. Stationery Office. 10*s.* 6*d.*

University of Cambridge

On Feb. 20 the degree of M.B. was conferred on A. J. Costello and E. H. Richards.

University of London

The following degrees have been awarded:

M.D.—P. A. Gardiner, Leslie Michaels, P. A. Zorab.
M.S.—Edward Parry-Jones.

University of Edinburgh

Dr. Talib Astarabadi has been appointed lecturer in the department of physiology.

University of St. Andrews

Next session a postgraduate course in the clinical and medical sciences will be held at Queen's College, Dundee, and in anatomy and physiology at St. Salvator's College, St. Andrews. Further particulars may be had from the dean of the faculty of medicine, Queen's College, Dundee.

Royal College of Surgeons of England

On Wednesday, March 9, at 4 P.M., Prof. F. Orban will give the Moynihan lecture. He will speak on new trends in the treatment of thrombo-angiosis (Buerger's disease). On Wednesday, March 16, at 4 P.M., Dr. J. Alfred Lee will give Joseph Clover lecture. His subject will be Joseph Clover and the Contributions of Surgery to Anæsthesia. On Monday, March 28, at 5 P.M., Dr. R. A. Weale will give the Edridge-Green lecture. He will speak on the duplicity theory of vision. All the lectures will be at the college, Lincoln's Inn Fields, London, W.C.2.

Institute of Almoners

The annual general meeting of this institute will be held on Friday, March 18, at Senate House, University of London, W.C.1, at 5.30 P.M. Dr. David Stafford-Clark will speak on the Doctor, the Patient, and the Public.

Christian Medical Fellowship

This fellowship will meet on Wednesday, March 16, at 8.15 P.M., at the Royal Commonwealth Society, Northumberland Avenue, London, W.C.2. Mr. A. S. Aldis will speak on Keeping Faith with the Patient.

Association of Industrial Medical Officers

A meeting of this association will be held on Friday and Saturday, March 25 and 26, at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1, and Guy's Hospital, London Bridge, S.E.1. The meeting will include a discussion on the work of the medical branch of the factory inspectorate of the Ministry of Labour and the speakers will be Dr. Sibyl Horner, Dr. A. T. Doig, Dr. S. G. Rainsford, and Dr. Ronald Owen. Further particulars may be had from the hon. secretary of the association, 47, Lincoln's Inn Fields, W.C.2.

Visiting Professors at the Postgraduate Medical School

The following professors from overseas are to take part in the work of the department of surgery of the Postgraduate Medical School of London this session:

Dr. S. R. Friesen, professor of surgery in the University of Kansas, who is spending a year in the department;

Mr. B. S. Rao, professor of operative surgery at Andhra Medical College, Visakhapatnam, India, who is spending a year;

Dr. M. K. Chachava, professor of surgery in the University of Tiflis, Georgia, U.S.S.R., who is spending three months.

Uganda's New Teaching Hospital

A grant of £1,230,000 for the new general teaching hospital at Mulago has been made under the Colonial Development and Welfare Acts.

The hospital is being built by the Protectorate Government, and when completed in 1964 it will have 758 beds and wards for 132 paying patients. The local specialist services will be based on it, and it will be the teaching hospital for Makerere College Medical School.

Commission for Comparative Neuroanatomy

This commission was founded, as part of the World Federation of Neurology, at a meeting of a group of comparative neuroanatomists held last November in Giessen.

Its main objectives are: to improve conditions for workers in this discipline; to catalogue and make more accessible existing collections of comparative neuroanatomical material, and to add new material; and to further the exchange of material and workers. Further particulars may be had from Dr. Heing Stephen, Max-Planck-Institut für Hirnforschung, Friedrichstr. 24, Giessen, Germany.

Mr. A. R. W. Bavin has been appointed under-secretary for finance and accountant general in the Ministry of Health. He succeeds Mr. A. S. Marre, who will now become responsible for health services remuneration, staffing, and superannuation.

Prof. John McMichael will be away from London from March 13 until July on a Sims professorial tour of Australia and New Zealand.

The Group for Representation of the Views of Clinical Psychiatrists will meet on Monday, March 21, at 5.30 P.M., at Tavistock House North, London, W.C.1.

Correspondence and inquiries about the first International Conference on Congenital Malformations, which is to be held in London from July 18 to 22, should be addressed to the secretariat of the conference, 67, New Bond Street (Dering Yard), London, W.1.

The Apothecaries' Hall Dispensers' Association hopes to start an employment agency for its members. The secretary, Miss E. Linton (65, Oak Road, Crumpsall, Manchester, 8), will be pleased to hear from anyone seeking the services of an Apothecaries' Hall dispenser, and will try to put them into touch with suitable candidates. There will be no charge for this service, but contributions towards postal expenses would be appreciated.

The annual dinner of the Indian Medical Association (Gt. Britain) will be held on Thursday, May 5, at the Cumberland Hotel, Marble Arch, London, W.1, at 8.15 P.M. Tickets (37*s.* 6*d.*) may be had from Dr. S. L. Karani, 273, Upton Road, Bexley, Kent.

CMF/MEF Physicians' dinner will be held at Simpson's-in-the-Strand, London, W.C.2, on Saturday, April 9, with Dr. E. R. Boland in the chair. Information can be had from Dr. A. Willcox, the hon. secretary, 59, Harley Street, W.1.

Gadgets for the Disabled.—The National Association for the Paralysed have bound together their leaflets dealing with such topics as aids for lifting, dressing, and bathing the patient, and gadgets to help him in eating, drinking, household work, recreations, and getting about. Copies of the complete set (10*s.* plus 6*d.* postage) or of separate leaflets (1*s.* each) may be had from the Association (1, York Street, Baker Street, London, W.1).

A subscriber who has a complete set of unbound issues of *The Lancet* from 1940 to 1959 would like to give them to the library of a Commonwealth medical school which could arrange for packing and transport.

Diary of the Week

MARCH 6 TO 12

Monday, 7th

UNIVERSITY COLLEGE, Gower Street, W.C.1
5 P.M. Dr. Antoinette Pirie: Biochemistry of the Eye. (Second of two lectures.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. J. C. White: Abnormal Hæmoglobins.
GUY'S HOSPITAL, S.E.1
5.30 P.M. Dr. A. T. Cowie: Gynæcomastia and Disorders of the Breast.
UNIVERSITY OF ST. ANDREWS
4 P.M. (Queen's College, Dundee.) Dr. H. B. Goodall, Dr. William Walker: Genetic Factors in Blood Disease.

Tuesday, 8th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Dr. J. D. N. Nabarro: The Pituitary and Adrenal Cortex in General Medicine. (First of two Oliver-Sharpey lectures.)
UNIVERSITY OF LONDON
5.15 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. Frederick Sanger: Aminoacid Sequences in Proteins. (First of two lectures.)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Experimental Medicine and Therapeutics.* Prof. W. D. M. Paton: Principles of Drug Action. (Presidential address.)
8 P.M. *Psychiatry.* Dr. Felix Brown: The Bereavement Factor in Depressive Illness. Dr. John Bowlby: Grief and Mourning in Infancy.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Mr. Aleck Bourne: Troubles of Puberty.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Mr. G. C. Knight: Cervical Spondylosis.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. G. A. Hodgson: Skin Hazards of Petroleum Engineering Oils.
BIRMINGHAM MEDICAL INSTITUTE, 36, Harborne Road, Edgbaston
8 P.M. *Psychiatry.* Dr. G. M. Carstairs: Recent Research on the Rehabilitation of Schizophrenic Patients.
MANCHESTER MEDICAL SOCIETY
8 P.M. (Medical School, University of Manchester.) *Surgery.* Mr. D. K. Lennox: Observations on the Obstructed Colon.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. Denis Williams: Syndromes of Basilar Insufficiency.

Wednesday, 9th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
4 P.M. Prof. F. Orban: New Trends in the Treatment of Thromboangiosis (Buerger's Disease). (Moynihan lecture.)
ROYAL SOCIETY OF MEDICINE
4.30 P.M. *Physical Medicine.* Dr. F. S. Cooksey: Progress and Problems in Rehabilitation of Disabled People. (Samuel Hyde lecture.)
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Antibiotics and Skin Infections.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. J. R. May: Considerations Regarding Immunity to *H. influenzæ.*
MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) *Pathology.* Dr. George Discombe: Observations on Iron Deficiency.

Thursday, 10th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M. Dr. Nabarro: The Pituitary and Adrenal Cortex in General Medicine. (Second of two Oliver-Sharpey lectures.)
ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Mr. S. O. Aylett: Diffuse Ulcerative Colitis and its Treatment by Ileo-rectal Anastomosis. (Hunterian lecture.)
ROYAL SOCIETY OF MEDICINE
5 P.M. *Ophthalmology.* Mr. H. B. Stallard, Mr. O. M. Duthie: Complications of Intra-ocular Surgery.
KING'S COLLEGE HOSPITAL MEDICAL SCHOOL, Denmark Hill, S.E.5
4.30 P.M. Dr. Terence East: Forty Years of Cardiology. (Wiltshire lecture.)
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. P. D. Samman: Tuberculosis of the Skin.
ALFRED ADLER MEDICAL SOCIETY
8 P.M. (1, Wimpole Street, W.1.) Dr. A. Spencer Paterson: The Conditioned Reflex in Psychiatric Treatment.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.15 P.M. (11, Chandos Street, W.1.) Dr. A. G. Signy: Modern Views on the Anæmias.
NORTH WESTERN THORACIC SOCIETY
5 P.M. (Clinical Sciences Buildings, York Place, Manchester.) Dr. George Simon: Radiological Changes in Heart-disease.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Prof. F. T. G. Prunty: Abnormalities in Hyperparathyroidism.

Friday, 11th

UNIVERSITY OF LONDON
5.15 P.M. (London School of Hygiene and Tropical Medicine.) Dr. Sanger: Aminoacid Sequences in Proteins. (Second of two lectures.)
5.30 P.M. (London Hospital Medical College, Turner Street, E.1.) Prof. D. E. Denny-Brown (Harvard): Nature of Polymyositis and Related Muscular Diseases.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. J. B. Pennybacker: Intervertebral Disc Lesions.
4 P.M. Dr. Fraser Roberts: Medical Genetics.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Mr. N. Asherson: Common Maladies of Childhood.